Biological modalities

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Biological modalities

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Maximilian Huber, December 2016

Introduction

This thesis is about biological modalities. Biological modalities are modalities such as necessity, possibility and counterfactuality applied to biologically salient entities such as ecosystems, populations, organisms, traits, cells or genes. For example, the authors of the standard textbook on molecular biology write that a "molecule like hemoglobin was necessary to allow multicellular animals to grow to a large size, since large animals could no longer rely on the simple diffusion of oxygen through the body surface to oxygenate their tissues adequately" (Alberts et al. 2008: 256). This claim contains three biological modalities: biological necessity (a molecule which carries oxygen from the respiratory organs to the rest of the body is biologically necessary in large multicellular animals), biological possibility (even though hemoglobin is the actual oxygen-carrying molecule in large multicellular animals, it is biologically possible that this function is carried out by a different protein), and biological counterfactuality (if large multicellular animals did not have an oxygen-carrying molecule, then they would not be viable). In what follows, I will take an epistemic perspective on biological modalities. That is, I am concerned with (conceptual) tools and heuristics aimed at better understanding the role of biological modalities in biological explanations.

This thesis has three parts. In chapters 1–3, I sketch a theory of biological modalities. In chapters 4–7, I provide an implementation based on a case study. Finally, in chapters 8 and 9, I discuss some applications. I will now provide a brief overview of each chapter.

In chapter 1, I motivate my research. I argue that there is a tension between (1) the lack of philosophical interest in biological modalities and (2) the important explanatory role biological modalities play in biological practice. The first claim is supported by a quantitative analysis of major academic databases and a qualitative survey of the philosophical literature. I defend the second claim by four 'arguments from case study' pertaining to coiled ammonoid shell form, sticky footpads and maximum body size, the minimal bacterial genome and essential genes, and the habitability of exoplanets. I

propose that a theory or logic of biological modalities could fill the epistemic lacunae between (1) and (2) by providing truth-conditions for biological modalities, shedding light on the relationship between biological and other modalities, and spelling out how biological modalities can be graded.

In chapter 2, I offer two main of clarifications of how (not) to think about biological modalities. First, I argue that defining biological possibility as non-violation of biological laws is problematic since it requires a commitment to both realism about biological laws and the better best systems account of special science laws; otherwise biological possibility is reduced to physical or logical possibility, or its definition is rendered circular. Second, I examine three ideas regarding the grading of (biological) possibility, namely (1) the distinction between kinds of possibility such as logical, physical and biological possibility and (2) between subkinds of biological possibility which roughly map to the scale of biological phenomena under investigation and come in historical or ahistorical flavors, and (3) the observation that some subkinds of biological possibility are comparative.

In chapter 3, I improve upon Daniel Dennett's (1995) definition of biological possibility by proposing two modifications. First, I provide a clarification of his definition by reconstructing the Library of Mendel as relational structure. Second, I argue that the most important shortcoming of Dennett's definition, namely the underdefined accessibility relation, can be overcome by interpreting the accessibility relation as a solution to a string editing problem. According to the restated definition, x is biologically possible with respect to a genome g if and only if there is some genome g' such that there is an edit script from g to g' that fits certain cost requirements given a set of edit operations, and x is an instance of g or a feature of the phenotypic products of g'. This new definition schema is promising because it is rooted in biological practice and can be extended into a family of modal logics.

In chapter 4, I propose to put into action the results obtained so far by constructing logical models of hemoglobin variants. Hemoglobin is the protein in red blood cells responsible for binding oxygen; normal adult hemoglobin consists of two alpha and beta globin chains determined by the hemoglobin alpha and beta gene respectively. The modeling goal is to attain the desiderata specified above (to wit, truth conditions, inferential relationships, grading). To this end, I present a schema for the classification of point mutations and impose three modeling restrictions: The hemoglobin variants must be caused by (1) single (2) substitutions (3) at codon 6 of the hemoglobin beta gene.

Finally, I briefly review why bioambient calculus, Zsyntax, and mathematical models in molecular biology are not suitable for the task at hand.

In Chapter 5, I introduce a simple model of hemoglobin variants caused by single substitutions at codon 6 of the hemoglobin beta gene within the framework of propositional modal logic. In the model, states are interpreted as codons, the binary relation is interpreted as single substitution, and the valuation is kept fixed and induces a partition of blocks of codons that code for some amino acid. I argue that explicit truth conditions for at least historical and ahistorical biological modalities are attained via the modal language describing the model. This gives rise to a normal modal logic that is sound and complete with respect to the class of serial, symmetric and dense frames. After showing that the model can be simplified via bisimulation contraction, I argue that the notion of silent mutation is ambiguous between mutants that are bisimilar to the wild type and hence modally silent, and mutants that are not and hence modally active.

In chapter 6, I extend the simple model and language to account for comparative (historical) biological possibility. This yields a ranking of hemoglobin variants $v, v', \ldots$ caused by single substitutions at codon 6 of the hemoglobin beta gene. I distinguish four circumstances under which v is more possible than v': (1) v is easier to bring about that v', implemented by a modal operator capturing Hamming distance. (2) There are more possible v than v', implemented by a modal operator counting variants. (3) There are more ways to realize v than v', implemented by a modal operator counting unique sequences of single substitutions. (4) v is more probable than v', implemented by a non-epistemic probabilistic modal operator and a weighted binary relation interpreted as single substitution. In addition, I discuss the conditions for the introduced modal operators' loss of historical or local context, and I show the extension's ability to incorporate transition/transversion bias or amino acid scoring matrices.

In chapter 7, I show that the previously imposed modeling restrictions can be lifted via a generalization of the simple model. This enables the construction of logical models of any protein variant caused by any point mutation at the coding region of any gene. In the generalized model, states are interpreted as genes, multiple binary relations are interpreted as distinct point mutations, and the valuation is kept fixed and induces a partition of blocks of genes that code for some protein. I identify two limitations, namely (1) the limited expressive power and (2) the reliance on opaque modalities of the language describing the generalized model.

In chapter 8, I present SMAC (Simple Model Amino acid Checker), a model checking

tool implemented in Python and made publicly available at maxghuber.github.io/SMAC under the Apache License. It allows the user to obtain the truth value of any formula ϕ of the basic amino acid language in the simple model. SMAC builds a semantic tree where the root is the codon of evaluation decorated with ϕ, descendants are codons decorated with subformulas of ϕ, and the leafs jointly comprise all logically possible truth makers of ϕ. Each branch is then evaluated bottom-up. I show that SMAC has the total correctness property, and that SMAC scales exponentially for nested modal operators where the exponent is given by the highest number of nested modal operators.

In chapter 9, I argue that the standard semantics of counterfactual conditionals are a bad fit for biological counterfactuals. The standard semantics require a similarity ordering of states which is explicated in terms of physical laws. However, such a similarity ordering is pragmatically unattainable, and even if it were attainable, it would still entail explanatory mismatches. As an alternative, I propose a similarity ordering in terms of edit distance that is easily computable. This yields semantics for at least some biological counterfactuals that does not rely on laws (physical or other). Finally, I show that these semantics can be seamlessly integrated with the semantics of the biological modalities introduced earlier.

I. Towards a theory of biological modalities

1. Motivation

The aim of this chapter is to motivate a theory of biological modalities. In section 1.1, I will show that very little theoretical work on biological modalities has been undertaken based on a quantitative analysis of academic databases. In section 1.2, I will argue biological modalities nevertheless play an important explanatory role in biological practice. To this end, I will examine four paradigmatic examples of biological research. Finally, in section 1.3, I will spell out a number of desiderata for a theory of biological modalities.

1.1 A lack of theory

In this section, I will argue that very little theoretical work on biological modalities has been undertaken based on a quantitative analysis of academic databases. The above discussion can hence be seen as a stand-in for a more classical review of the literature that can be usually found at this place.

In order to do so, I have conducted a series of queries about biological, physical and logical modalities on a range of databases that jointly represent academic publishing. Before presenting and interpreting the obtained results in subsection 1.1.2, the databases are presented and it is explained how the modalities under consideration have been operationalized in subsection 1.1.1.

1.1.1 Methods

I compiled data from nineteen popular and/or renowned academic databases summarized in Table 1.1. These fall into three categories: Multidisciplinary databases (CiteSeerX, Google Scholar, JSTOR, ProQuest Dissertations & Theses Database, Microsoft Academic, ScienceDirect, Science.gov, SpringerLink, Web of Science, Wiley Online Library,

Database	URL	Category	OA	Description
Academia	academia.edu	Social	✗	>35.8m members
BioOne	bioone.org	Biology	✓	>190 journals
CiterSeerX	citeseerx.ist.psu.edu	General	✓	>6m entries
Google Scholar	scholar.google.com	General	✓	based on Google search engine
JSTOR	jstor.org	General	✓	>240 journals, >40000 books
Philosopher's Index	philindex.org	Philosophy	✗	>0.6m entries, >1700 journals
PhilPapers	philpapers.org	Philosophy	✓	>1.8m entries, >1000 journals
PLOS	plos.org	Biology	✓	>0.14m entries
PQDT	search.proquest.com	General	✗	>2.3m entries (i.e., dissertations and theses)
Microsoft Academic	academic.microsoft.com	General	✓	>80m entries
NCBI	ncbi.nlm.nih.gov	Biology	✓	>300m entries
ResearchGate	researchgate.net	Social	✗	>9m members, >80m entries
ScienceDirect	sciencedirect.com	General	✓	Elsevier owned; >2500 journals, >33000 books
Science.gov	science.gov	General	✓	>200m entries
SpringerLink	link.springer.com	General	✓	Springer owned; >9m entries, >3200 journals
SEP	plato.stanford.edu	Philosophy	✓	>1500 entries
Web of Science	webofknowledge.com	General	✗	Thomson Reuters owned; >1000m entries
Wiley Online Library	onlinelibrary.wiley.com	General	✗	Wiley-Blackwell owned; >6m entries, >1500 journals
WorldCat	worldcat.org	General	✓	>330m entries

Table 1.1

Nineteen popular and/or renowned academic databases that jointly represent academic publishing. OA indicates whether or not the database is open access (and not whether the elements in the database are open access); an entry can be a journal article, book, or any other kind of scientific publication depending on the database. All information as provided on the respective web pages on April 13, 2016.

WorldCat), social databases (Academia, ResearchGate), and domain specific databases, namely biological databases (BioOne, PLOS, NCBI) and philosophical databases (Philosopher's Index, PhilPapers and Standford Encyclopedia of Philosophy). I submit that these databases are jointly representative of how academics (and in particular, biologists and philosophers) publish their findings respectively how their publications can be accessed. To wit, try to find a post-1900 publication that is not in at least one of these databases. This should prove to be extremely difficult since the most important academic publishers are covered (see Larivière et al. 2015), open access publishing is covered, social or informal publishing is covered, and the most important databases for biology respectively philosophy are covered (however, non-indexed contributions to small conferences or workshops could for example fall through the cracks).

These nineteen databases were then canvassed for biological, physical and logical modalities. In order to do so, the kinds modalities under consideration had to be operationalized. Since all databases allow for exact search queries, each kind of modality was represented as set of strings. For example, consider the operationalization of biological modality:

$$\mathrm{BM} = \mathrm{BP} \cup \mathrm{BN} \tag{1.1}$$

$$\mathrm{BP} = \{\text{'biological possibility'}, \text{'biologically possible'}\} \tag{1.2}$$

$$\mathrm{BN} = \{\text{'biological necessity}, \text{'biologically necessary'}\} \tag{1.3}$$

In what follows, I will abbreviate the operationalization of biological modality as BM, and the operationalization of physical and logical modalities as PM and LM respectively. Note that PM and LM are defined analogously to BM as per (1.1)–(1.3). The obtained data could be improved by adding to each operationalization further inflections and variants of the modalities under consideration. For example, BM could be improved by adding the strings 'biological possibilities' (plural), 'biologically impossible' (negation), and so on. An easy way to achieve this would be via wildcard characters. However, not all databases have search masks that allow for (compound) wildcard characters which is why wildcard characters have not been implemented here.

In addition to the operationalzation, for each database, a search query had to be defined given the syntax of the corresponding search mask. In all cases, whenever possible, the search query forces a maximally inclusive full-text search. The search queries are summarized in in Table 1.2.

Database	Query syntax	Comment
Academia	‘`string`’ site:academia.edu	On google.com since Academia is unsearchable
BioOne	All: ‘`string`’	
CiteSeerX	‘`string`’	
Google Scholar	‘`string`’	Results exclude patents and quotes
JSTOR	‘`string`’	
Philosopher’s Index	‘`string`’.mp	On ovid.com
PhilPapers	‘`string`’	Maximum of 1000 results
PLOS	everything:‘`string`’	
ProQuest	‘`string`’	
Microsoft Academic	‘`string`’	Semantic search
NCBI	‘`string`’[all fields]	Manual aggregation over all databases
ResearchGate	‘`string`’ site:researchgate.net	On google.com since ResearchGate is unsearchable
ScienceDirect	‘`string`’	
Science.gov	Full Record: ‘`string`’	Results exclude DOE Data Explorer, DOEpatents, ESTSC, NASA, and US Patent databases due to time out error
SpringerLink	‘`string`’	
SEP	‘`string`’ site:plato.stanford.edu	On google.com for more accurate results
Web of Science	‘`string`’	
Wiley Online Library	‘`string`’	
WorldCat	kw:‘`string`’	

Table 1.2

Search query syntax for all input strings (denoted by `string`). If not indicated otherwise, the most inclusive search was performed (e.g., search over all entries instead of accessible entries; full text search instead of search in abstracts only; etc.).

With the databases, the operationalization of the kinds of modalities and the query syntax in place, the frequencies of each kind of modality for each database can be computed in a straightforward manner:

$$\mathrm{F(BM)} = \sum_{x \in \mathrm{BM}} \mathrm{F}(x) \tag{1.4}$$

where $\mathrm{F}(x) \in \mathbb{N}$ is given by a search of string x in the database given the corresponding query syntax as specified in Table 1.2. Then $\mathrm{F}(x)$ is the frequency of the string in the database and F(BM) is the aggregate frequency of all strings in BM in the database.

A final component is yet missing: In order to allow for a comparison of frequencies across databases, they need to be normalized. This can be achieved by using an extremely common string as baseline. Using again BM as an example for some database, the normalized frequency of BM, denoted by N(BM), is given as follows:

$$\mathrm{N(BM)} = \frac{\mathrm{F(BM)}}{\mathrm{F(baseline\ string)}} \tag{1.5}$$

So the normalized frequency is the ratio of the frequency to the baseline string for each database. According to the Oxford English Corpus, 'time' is the most common English noun and hence an ideal baseline string (for more details on the Oxford English Corpus, see Culpeper 2009). However, there are more than fifty particles, short verbs and adjectives that are more common; so why use 'time'? There are three pragmatic reasons: Many databases have search masks that 1. have a minimum string size that excludes most particles, 2. exclude logical connectives such as 'and' from being searched because they are part of the search mask's syntax, or 3. return results for strings such as 'be' or 'the' that are implausibly low. In light of these reasons, (1.5) can be adapted accordingly:

$$\mathrm{N(BM)} = \frac{\mathrm{F(BM)}}{\mathrm{F(`time')}} \tag{1.6}$$

And similar for PM and LM.

1.1.2 Results and discussion

I will now turn to present the results. There are two main findings:

1. The frequency of BM is low.

Database	F(BP)	F(BN)	F(PP)	F(PN)	F(LP)	F(LN)	F('time')
Academia	554	1095	5785	1398	8140	5400	629000
BioOne	22	10	30	4	29	16	114630
CiteSeerX	1298	627	16398	1193	17434	4772	4642595
Google Scholar	1225	9200	53180	11820	69900	56400	6450000
JSTOR	489	1422	5125	2571	14648	12928	5701480
Philosopher's Index	4	11	56	50	385	358	26959
PhilPapers	3	4	58	53	172	198	1000
PLOS	86	15	102	6	88	10	161589
ProQuest	6	13	64	21	87	98	83407
Microsoft Academic	8557	1967	9136	3657	1479	882	7703
NCBI	296	253	60	79	242	231	39103967
ResearchGate	1149	1191	10810	1351	10080	3600	14100000
ScienceDirect	529	586	5774	700	3805	1999	9325482
Science.gov	844	597	1599	999	1301	1047	2889
SpringerLink	573	806	6395	1618	10808	6853	5991573
SEP	6	8	91	23	222	170	3180
Web of Science	75	53	376	53	232	211	13766290
Wiley Online Library	477	663	2944	780	4639	3435	4596552
WorldCat	189	261	2984	345	1113	1121	22343288

Table 1.3

Frequencies of kinds of modalities in sample databases as per April 13, 2016.

2. The frequency of BM is lower than the frequency of each of PM and LM.

Let me discuss these results in turn. I begin with the first result. The absolute frequencies of BM, PM, LM and 'time' are summarized in Table 1.3. Two remarks about the quality of the reported data are in order. First, there are data points which are easily identified as artifacts. For example, PhilPapers, Microsoft Academic, and Science.gov have all implausibly low results for 'time', although for different reasons: While PhilPapers simply does not quantify results over a certain threshold, Microsoft Academic and Science.gov employ a semantic respectively thematic search. That is, in both cases, the input string 'time' is interpreted as a query about a category rather than an exact match. Artifacts like these are easily caught via the Anderson-Darling test discussed below. Second, it is important to underscore that an absolute frequency of $n \in \mathbb{N}$ for a kind of modality, say BP, does not mean that there are n publications about biological possibility in the corresponding database. More precisely, in order for a publication to be counted as result, it is sufficient that any string in the set BP is mentioned; hence, it is not necessary that the notion of biological possibility is defined and/or explained in the publication. There are at least two methods to improve upon the data; that is, there are

at least two methods to increase the chance that the modal notion under consideration is indeed defined and/or explained in the publication:

1. The frequency of 'biological possibility' (and 'biologically possible') with respect to a publication can be used as a proxy for the degree to which the publication is about biological possibility. Put differently, the higher the frequency 'biological possibility' (and 'biologically possible') for a given publication, the higher the chance that the publication provides a definition and/or explanation of biological possibility. For example, there are 23 mentions of 'biological possibility' and 7 mentions of 'biologically possible' but no mention of either 'biological necessity' and 'biologically necessary' in the book of Dennett (1995) which I have claimed to provide the only explicit definition and explanation of biological possibility. However, an implementation of such a quantitative strategy is not feasible since none of the search masks of the selected databases allow for this kind of second order search, and, more importantly, all publications would need to be available for a full-text search (which is not the case).

2. A more qualitatively oriented strategy is to manually screen and evaluate the publications yielded by the query. However, this is extremely labor intensive, and again all publications would need to be available (which is still not the case). While I have manually checked the first dozen or so results for each database and string in BP with the result of not finding any publication about the notion of biological possibility in the required sense, this is merely anecdotal given the number of results returned for some databases. For now, simply note that the sum of results for BM over all three philosophical databases amounts to only 36 (including duplicates), only one of which provides a definition and/or theory in the required sense; so at least for the philosophical databases, most results are false positives.

In short, the reported low frequency of BM indicates an ever lower number of publications that actively engage with biological modalities instead of merely employing them.

I will now turn to the second result. The normalized frequencies of BM, PM and LM are summarized in Table 1.4. Since we are not interested in absolute frequencies, data cleansing proves to be much easier in this case. In order to catch outliers, we check for each kind of modality whether the normalized frequencies over all databases adhere to a normal distribution. For this the Anderson-Darling test is used; the minimum number of outliers is then removed (see Kvam and Vidakovic 2007: 90ff. for details). Note that in all cases in which the validity of a data point was challenged with respect to abso-

Database	N(BP)	N(BN)	N(PP)	N(PN)	N(LP)	N(LN)
Academia	~~0.000881~~	~~0.001741~~	~~0.009197~~	~~0.002223~~	~~0.012941~~	~~0.008585~~
BioOne	0.000192	0.000087	0.000262	0.000035	0.000253	0.000140
CiteSeerX	0.000280	0.000135	~~0.003532~~	0.000257	0.003755	0.001028
Google Scholar	0.000190	~~0.001426~~	~~0.008245~~	~~0.001833~~	~~0.010837~~	~~0.008744~~
JSTOR	0.000086	0.000249	0.000899	0.000451	0.002569	0.002267
Philosopher's Index	0.000148	0.000408	0.002077	~~0.001855~~	~~0.014281~~	~~0.013279~~
PhilPapers	~~0.003000~~	~~0.004000~~	~~0.027000~~	~~0.031000~~	~~0.058000~~	~~0.042000~~
PLOS	~~0.000532~~	0.000093	0.000631	0.000037	0.000545	0.000062
ProQuest	0.000072	0.000156	0.000767	0.000252	0.001043	0.001175
Microsoft Academic	~~1.110866~~	~~0.118006~~	~~0.137349~~	~~0.255355~~	~~0.739063~~	~~0.446969~~
NCBI	0.000008	0.000006	0.000002	0.000002	~~0.000006~~	~~0.000006~~
ResearchGate	0.000081	0.000084	0.000767	0.000096	0.000715	0.000255
ScienceDirect	0.000057	0.000063	0.000619	0.000075	0.000408	0.000214
Science.gov	~~0.292143~~	~~0.206646~~	~~0.256490~~	~~0.296989~~	~~0.553479~~	~~0.173416~~
SpringerLink	0.000096	0.000135	0.001067	0.000270	0.001804	0.001144
SEP	~~0.001887~~	~~0.002516~~	~~0.028616~~	~~0.007233~~	~~0.069811~~	~~0.053459~~
Web of Science	0.000005	0.000004	0.000027	0.000004	0.000017	~~0.000015~~
Wiley Online Libary	0.000104	0.000144	0.000640	0.000170	0.001009	0.000747
WorldCat	0.000008	0.000012	0.000134	0.000015	0.000050	0.000050

Table 1.4

Normalized frequencies of kinds of modalities in sample databases as per April 13, 2016. Crossed-out values indicate non-normally distributed normalized frequencies per column as determined by the Anderson-Darling test.

lute frequencies, the corresponding normalized frequencies are marked as outliers. The averages over all databases of the clean normalized frequencies are detailed in Figure 1.1.

To sum up this section, I have argued that there is a lack of theory with respect to biological modalities based on a quantitative analysis of academic databases. I have presented two results in support of this claim: First, the number of publications that define and/or explain biological modalities is extremely low. And, secondly, the low standing of work on biological modalities as compared to work on physical and logical modalities. This completes the first section of this chapter. In section 1.2, I will argue that even if there is a lack of theory, biological modalities still play an important explanatory role in biological practice. In section 1.3, I will then spell out a number of desiderata for a theory of biological modalities.

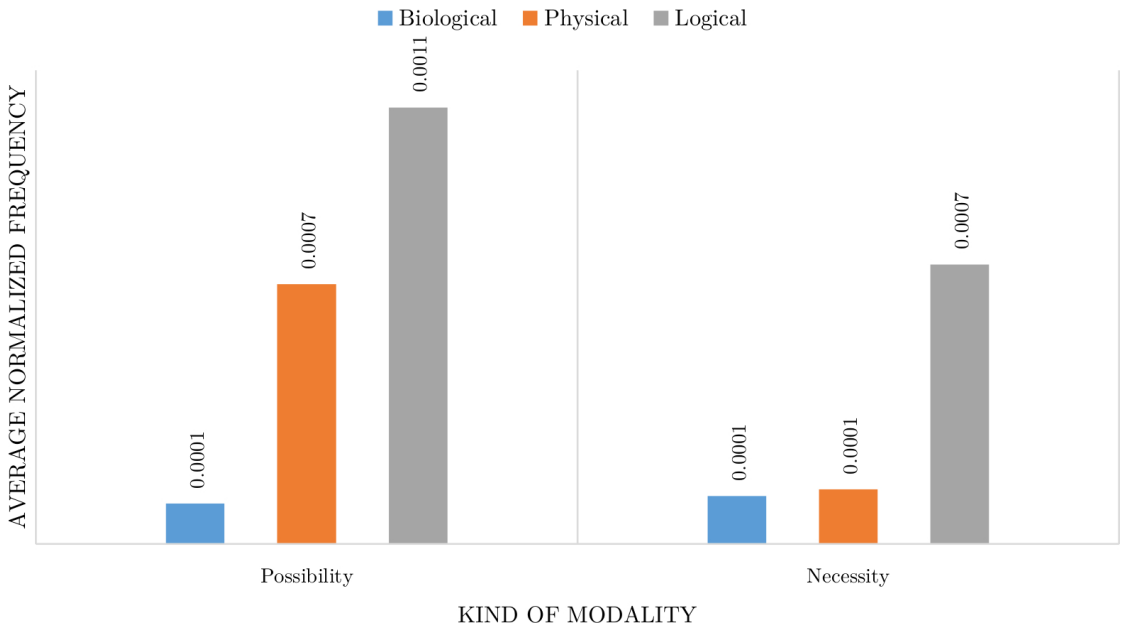


Figure 1.1
Histogram of the average normalized frequencies of biological, physical and logical modalities with respect to the sample databases.

1.2 Biological modalities are explanatory

Above I have argued that there is a lack of theory with respect to biological modalities. In this section, I will argue that biological modalities play an important explanatory role in biological practice based on an analysis of four cases, namely the computational model of coiled ammonoid shell form by David Raup (1962, 1966, 1967), the investigation of sticky footpads and maximum body size by David Labonte et al. (2016), the design and synthesis of a minimal bacterial genome by Clyde Hutchison et al. (2016), and the review of habitability by Charles Cockell et al. (2016). This motivates, in part, the construction of a theory of biological modalities which is undertaken in later chapters. In passing, I will then identify a number desiderata for such a theory which will be compiled in the next section.

The kind of argument employed in what follows could be dubbed 'argument from case study' (or AC in short). It is instructive to consider its form:

1. A case x is representative of a scientific domain D.
2. A proposition p holds in x.

$\therefore$ Therefore, p holds in D.

AC is an inductive argument and hence fallible. The strength of the support for the conclusion is given by the fit of the case to the scientific domain. That is, the better a case represents a scientific domain, the higher the chance that the truth of the proposition in question carries over to the scientific domain. Here is how AC is applied to the task at hand:

1. A case x is representative of biology.
2. Biological modalities play an important explanatory role in x.

$\therefore$ Therefore, biological modalities play an important explanatory role in biology.

Note that there might be a number of general epistemic issues related with this line of reasoning; I am not interested to discuss these here (but note that instances of AC are ubiquitous in philosophy of biology).[1] Rather, I will focus on two specific worries which I will discuss in turn:

The first worry is that the domain of biology is too large and heterogeneous, ranging from astrobiology to zoology. So a case study in one subfield tells us relatively little about biology or removed subfields. For example, a case study in molecular biology tells us relatively little about the use of biological modalities in (say) ecology. In order to address this worry, I will conduct more than one case study. In particular, I will consider four cases which jointly cover astrobiology, biomechanics, ecology, evolutionary biology, molecular biology, synthetic biology, and theoretical morphology.[2]

The second worry is that it is not clear what it means for a case to be representative of biology respectively the identified subfields. Marie Kaiser (2013) distinguishes three classes of cases (or paradigmatic examples) that are representative of biological practice; building on this distinction, we have:

1. Historical cases in the sense of field-defining research. Impact factor, number of citations, and so on, act as proxy for identifying such examples.
2. Textbook cases comprising results found in most or all standard textbooks.

[1] While this does not prove the epistemic merit of AC, it provides a pragmatic reason for employing AC.

[2] Here I simply group the cases into the self-identified subfields and neither presume that these subfields are discrete nor that the employed categorization has any metaphysical or epistemic import above common usage.

Case	Subfields	Class
Raup (1962, 1966, 1967)	Theoretical morphology	Historical case
Labonte et al. (2016)	Evolutionary biology, biomechanics	Cutting edge research
Hutchison et al. (2016)	Molecular biology, synthetic biology	Cutting edge research
Cockell et al. (2016)	Astrobiology, ecology	Cutting edge research

Table 1.5
The four analyzed cases, the subfields they represent and their kind of representation.

3. Cutting edge research as defined by recent publications in leading journals (or presentations at important conferences, and so on).

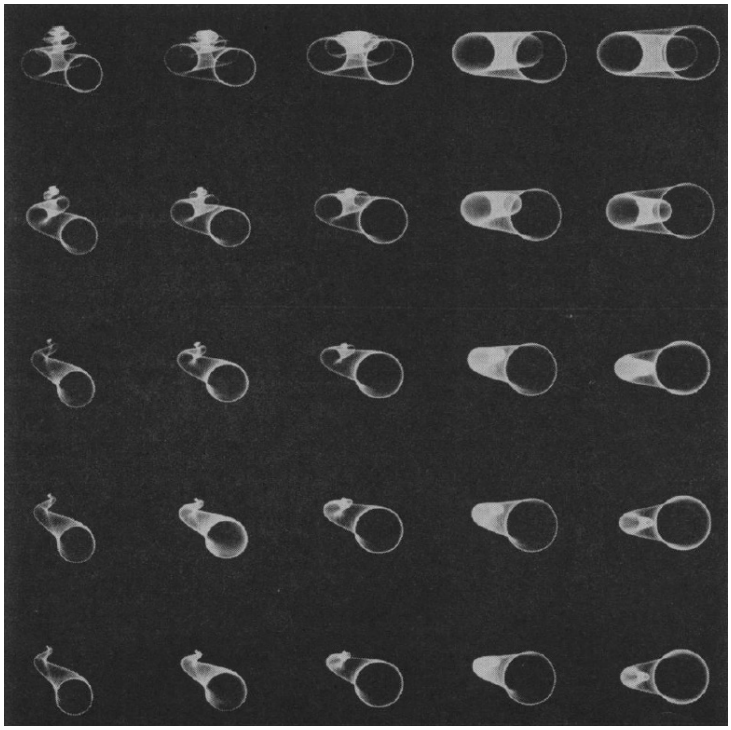
Two remarks are in order. First, these classes are not discrete since many historical examples will end up in textbooks, some cutting edge research will prove to be historical, and good textbooks incorporate cutting edge research. For example, in molecular biology, the discovery of the double-helix structure of DNA by Watson and Crick (1953) is a historical case; the mechanism of oxidative phosphorylation as explained by Alberts et al. (2008) is a textbook case; and any contribution in the latest issue of the Journal of Molecular Biology is an example of cutting edge research. Second, of the four cases to be discussed below, three are cutting edge research and one is a historical case. The reason for this selection is to ensure the novelty of the discussion and results. For a summary of the cases, see Table 1.5.

With AC in place, I will now turn to argue that biological modalities play an important explanatory role in the selected cases. By AC, this will show that biological modalities play an important explanatory role in the corresponding subfields of biology.

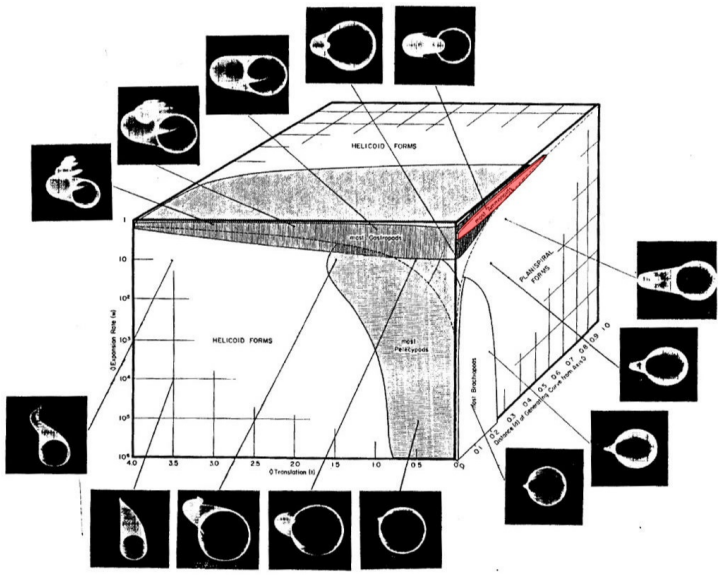
1.2.1 Coiled ammonoid shell form

David Raup's computational model of coiled ammonoid shell form is a classical example in what is sometimes called 'theoretical morphology' and has been discussed at length, for example by Richard Dawkins (1996: chapter 6) and George McGhee (2007). For this reason, I will abstain from an extensive exposition and focus on the role of biological modalities in Raup's research.

Ammonoids are a group of extinct marine cephalopod molluscs comprising more than 3700 species (Wiedmann and Kullmann 1996). The shells of ammonoids are coiled



(a) Coiled shell form simulated by the analog computer PACE TR-10.



(b) Three dimensional morphospace of coiled shell form. The small red area indicates the region occupied by ammonoids.

Figure 1.2

Coiled shell form simulation and morphospace (Raup and Michelson 1965; Raup 1966). The shells are transverse to the plain of coiling.

(spiral-like) and there is significant interspecific variation of shell form. In the 1950s and early 1960s, several mathematical models of coiled shell growth were proposed (Fukutomi 1953; Owen 1953; Rudwick 1959; Stasek 1963). Raup (1962, 1966, 1967) and Raup and Michelson (1965) were the first to provide a computational model (or computer simulation) of coiled shell growth. Here the coiled shell is modeled as hollow cone revolving around a fixed axis in a cylindrical coordinate system. The form of the shell is determined by four variables:

1. The shape of the base of the cone,
2. the expansion rate of the cone per revolution around the coiling axis,
3. the distance between the cone and the coiling axis, and
4. the translation rate of the cone along the coiling axis.

By systematically varying the values of these variables, the range of possible coiled shell form can be simulated. Figure 1.2a shows how this range can be graphically represented. But what notion of possibility is in play here? Raup uses at least three notions, namely "theoretically possible" (1965: 1294), "geometrically possible" (1966: 1178) and "physically possible" (1966: 1178). It is not clear whether Raup takes these notions have distinct meanings or whether he simply uses them as rhetorical device to draw a contrast to what is biologically possible. For note that each of the three notions disregard biologically salient information with respect to the animal's evolvability, development, fitness, and so on.

The range of thus possible coiled shell form is called the morphospace of coiled shell form.[3] Only a small region of the morphospace of coiled shell form is (or rather, was) actually occupied by ammonoids as detailed in Figure 1.2b. For example, ammonoids are not found in the region of overlapping coiled shell form. Raup suggests that empty regions exhibit "physiologically impossible" (1966: 1185) shell forms respectively shell forms "which are geometrically possible but biologically impossible" (1965: 1294). However, he does not tell us what he means by these notions of impossibility expect for the trivial fact that they refer to non-actual shell forms.

Now, with the morphospace of coiled shell form in place, let me submit two observations. First, modalities play an important explanatory role in constructing the morphospace

[3] 'Morphospace' is sometimes also called 'phenotypic space' (e.g., Alberch 1989 and Klingenberg 2005) or 'design space' which Sterelny and Griffiths (1999) attribute to Dennett (1995). However, as will be shown in chapter 3, the notion of design space is defined in terms of logical (and not theoretical, geometrical or physical) possibility.

of coiled shell form: Non-biological possibility serves as limit to the kinds of ways in which the values of the variables determining shell form can be varied, and the notion of biological (im)possibility is used as explanans for the absence of certain coiled shell forms from the fossil record. Second and less central to the line of attack of this section, Raup uses a variety of distinct notions of possibility, namely biological, physiological, geometrical, theoretical and physical possibility. However, aside from some implicitly assumed intuitive understanding, he neither makes explicit the meaning of the used grades of possibility nor how these grades are interrelated.

1.2.2 Sticky footpads and maximum body size

In a recent study, David Labonte et al. (2016) investigate the relationship between sticky footpads and body size in more than 250 species. Sticky footpads enable animals such as mites or geckos "to climb smooth vertical or inverted surfaces, thereby opening up new habitats" (Labonte et al. 2016: 1297). Now, is a gecko simply a scaled up mite, and how large could such an animal grow? In order to scale up and conserve an animal's ability to climb vertically via its sticky footpads, the mass m of the animal must be kept proportional to the maximum force F acting on the sticky footpads. This is expressed by (adapted from Labonte et al. 2016: 1297):

$$F = A\sigma \tag{1.7}$$

$$m \propto A\sigma \propto m^a m^b \tag{1.8}$$

where:

- A is the surface area of the adhesive pad,
- σ is the maximum adhesive stress, and
- a, b are scaling coefficients for A and σ respectively such that $a + b \approx 1$.

Now consider the following argument:

> If animals maintain geometric similarity when increasing in size, A would scale as $m^{\frac{2}{3}}$, so that the adhesion per body weight for large geckos ($m \approx 100$ g) is expected to be approximately $10^{\frac{7}{3}} \approx 200$ times smaller than for tiny mites ($m \approx 10$ µg) if the pads' adhesive strength σ remained unchanged ($b = 0$) (Labonte et al. 2016: 1297).

Let me provide a reconstruction of this argument: If we assume that $a = \frac{2}{3}$ and $b = 0$, then scaling up animals violates (1.8). That is, if an animal is scaled up geometrically, its mass increases much faster than the surface area of its sticky footpads (see appendix A. for details on geometric scaling); and if the maximum adhesive stress is not increased but kept constant, then the scaled-up sticky footpads are too weak to support the scaled-up animal's climbing ability. In short, if a mite is scaled up to the size of a gecko, it will fall off vertical surfaces. However, geckos (usually) do not fall off walls; so there must be ways in which animals can be scaled up in compliance with (1.8). Labonte et al. (2016: 1297) identify two such ways:

$$a > \frac{2}{3} \tag{1.9}$$

$$b > 0 \tag{1.10}$$

(1.9) states that the sticky footpad is scaled up faster than the rest of the animal's body. As a result, the footpad's disproportionately large surface area can compensate for the animal's increase in mass. By contrast, according to (1.10), the adhesive property of the sticky footpad is increased. As a consequence, the footpad can support more mass per unit of surface area. Labonte et al. find evidence for both evolutionary strategies in their dataset; I will briefly review them in what follows. With respect to (1.9), Labonte et al. find that $a = 1.02$ across all taxa and hence an "extreme positive allometry" (2016: 1298) of sticky footpad area. This means that the larger an animal, the larger the surface area of its sticky footpads as compared to the animal's total surface area as shown in Figure 1.3. However, turning now to (1.10), the allometry is less extreme for closely related taxa; here $b > 0$ and $a < 1.02$, that is an increase in the adhesive property of the sticky footpad but a more conservative (that is, geometric) ratio of footpad area to total body surface is observed. Labonte et al. explain this finding in terms of "anatomical constraints" (2016: 1299).[4]

Labonte et al. then derive an argument for the size limits of animals that rely on sticky footpads for climbing. They write:

> Scaling up the relative pad area of arthropods and small vertebrates to a human of 180 cm body length and 80 kg body mass would result in an adhesive pad area of $\approx 10^{6.91} \times 80000^{1.02} \approx 0.81$ m^2, approximately two-fifths of the total available body surface area [of approximately 2 m^2]. The required mor-

[4] What this means, I take it, is that an increase of b is in some sense more possible than an increase in a.

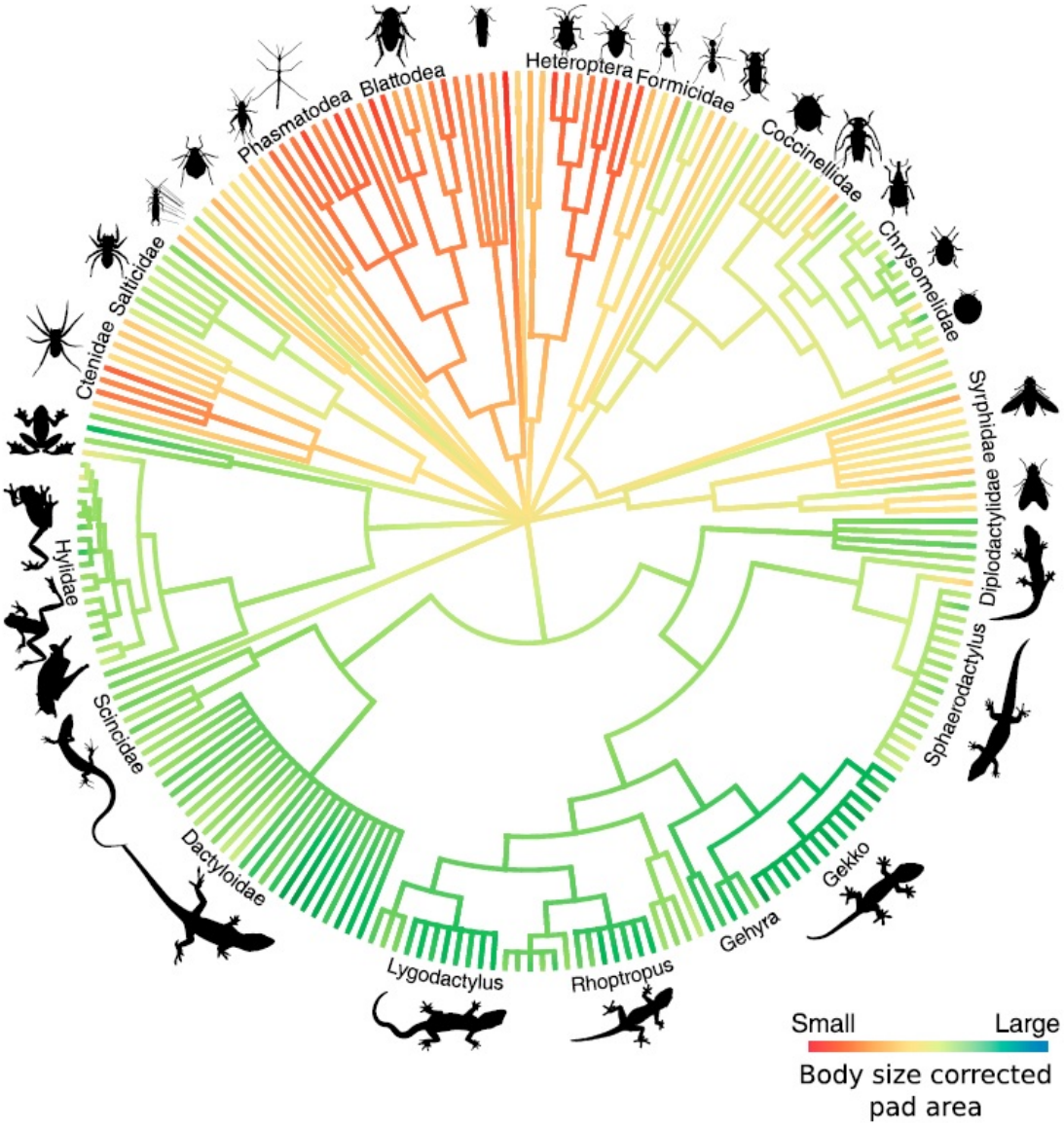


Figure 1.3

Scaling of sticky footpads in 250 species (Labonte et al. 2016: 1299). The larger an animal, the larger the surface area of its sticky footpads as compared to the animal's total surface area.

> phological changes, if at all possible, would thus be enormous, and difficult to achieve over short evolutionary timescales. Our results therefore indicate that phylogenetic inertia restricts the 'design space' for evolution at least for closely related taxa (Labonte et al. 2016: 1298).

Note that an explicit size limit is not mentioned. It is hence instructive to unpack this argument step by step. Labonte et al. first calculate that humans would need to have enormous hands and feet in order to be able to climb like geckos; this assumes adhesive pads at the endpoints of our limbs and the empirically determined scaling coefficient for the surface area of said adhesive pads. They then provide two reasons for why this is impossible. First, the morphological change is either impossible or too big. Second, the morphological change requires (too) much evolutionary time. Surprisingly, Labonte et al. do not mention a third reason, namely conceivable trade-offs, for example between hand surface area and dexterity, and a corresponding decrease in overall fitness.

Let us consider the first reason in more detail. Here it is again unclear what kind of possibility is in play. For example, the logical limit for adhesive pad area is half the animal's total surface area T:

$$A \leq \frac{T}{2} \tag{1.11}$$

To see this, consider an infinitesimal flat animal with a front and a back side such that

$$T = T_F + F_B \tag{1.12}$$

$$T_F = T_B \tag{1.13}$$

where T_F is the front surface area and T_B is the back surface area. In accordance with (1.11), assume that the whole front surface area constitutes the animal's adhesive pad:

$$A = T_F \tag{1.14}$$

The crucial observation is that the effective adhesive pad area A cannot be increased by making the back surface area of the animal sticky. That is, for every unit of T_F that attaches to a flat surface, a unit of T_B cannot attach to the same surface. Now, real animals are of course not infinitesimal flat. So the physical or biological limit for adhesive pad area is given by must be strictly smaller than $\frac{T}{2}$; see Figure 1.4 for size limits of adhesion-based climbing derived from the logical and a (hypothetical) biological limit for adhesive pad area.

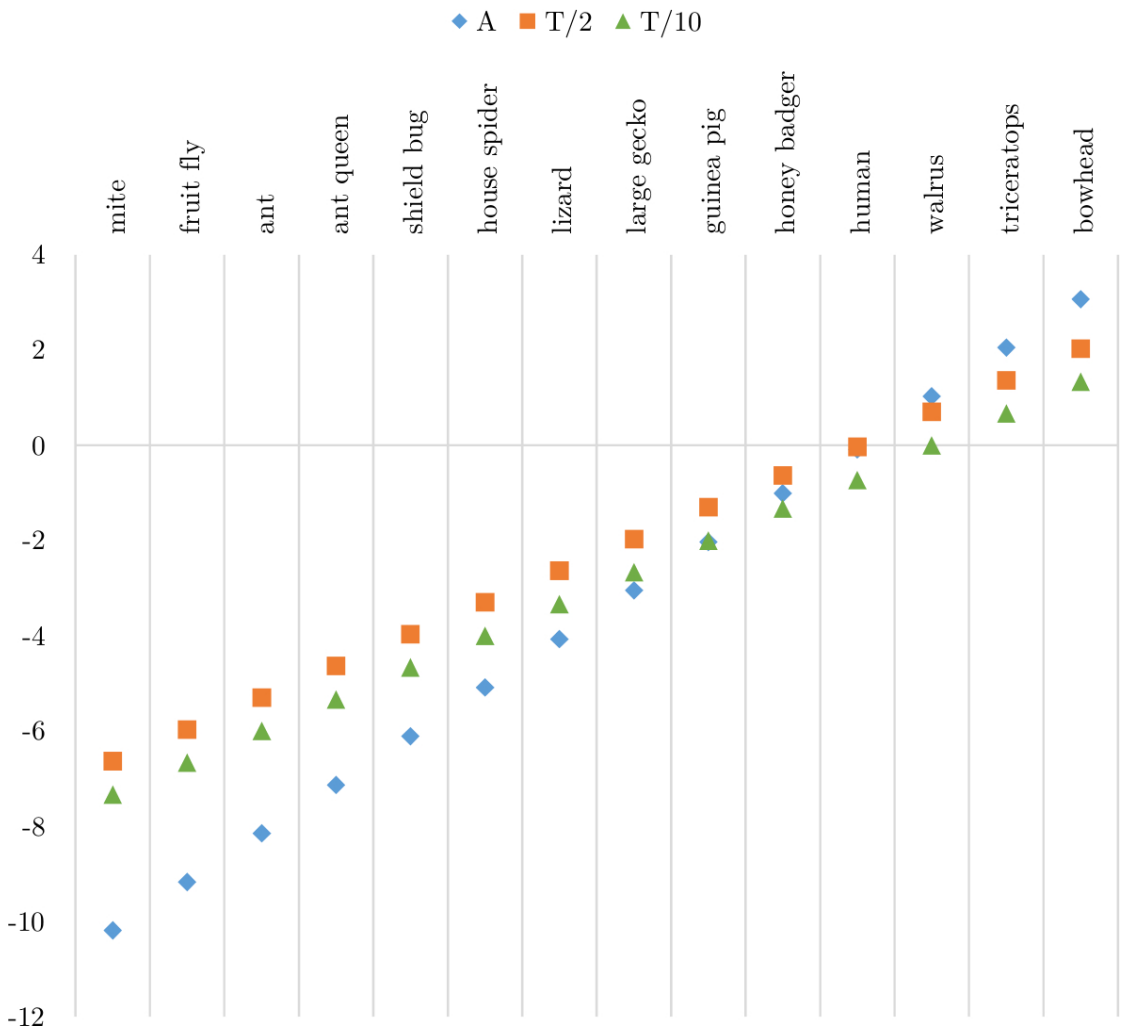


Figure 1.4

Size limits of adhesion-based climbing. This graph shows the relation between adhesion pad surface area A (blue) and two different size limits based on total body surface area T for different animals, namely the logical limit $\frac{T}{2}$ (orange), a hypothetical biological limit $\frac{T}{10}$ (green). For readability, all values are given as $\log_{10}$ transformation. If blue is below orange on the y-axis, then the animal on the x-axis is logically possible; and similar for green. For example, a walrus-sized animal that climbs via sticky footpads is neither logically nor biologically possible; a honey badger-sized animal is logically possible but biologically impossible; and a gecko-sized animal is both logically and biologically possible. A in square meters is given by $10^{6.91} \times m^{1.02}$ where m is mass in grams (see Labonte et al. 2016: 1298); T is roughly calculated as $m^{\frac{2}{3}}$ (see Wang and Hihara 2004 for more refined methods).

I will now turn to briefly comment on the explanatory role of biological modalities in this paper. First, Labonte et al. rely on counterfactual reasoning. To wit, mites the size of geckos or humans with hands and feet the size of baking trays are counterfactual animals. What is more, the above argument to the effect that adhesion-based climbing is impossible for humans perhaps even qualifies as biological thought experiment in the sense of Guillaume Schlaepfer and Marcel Weber (forthcoming).[5] Second, the size limits of adhesion-based climbers are explained in terms of which a certain ratio of adhesive pad to total body surface is 1. morphologically possible, 2. not restricted by phylogenetic inertia, 3. not excluded by anatomical constraints, and similar notions. I submit that 1.-3. are instances of a kind of biological possibility which I will discuss below under the heading of biohistorical possibility in chapter 2.

1.2.3 Minimal bacterial genome and essential genes

In a recent paper, Clyde Hutchison and his colleagues (2016) claim to have designed and synthesized a minimal bacterial genome (MBG) called JCVI-syn3.0. Before taking a closer look at their result and method, I will first clarify the meaning of MBG.

Intuitively, MBG is the smallest viable genome for a bacterium. However, it is important to distinguish two slightly more involved ways in which Hutchison et al. employ this notion:

1. MBG is a genome consisting of genes that are all essential for life.
2. MBG is the smallest genome that enables autonomous growth and replication.

Two remarks are in order: First, both definitions (and also the intuitive notion) are used interchangeably.[6] Second, Hutchison et al. (2016: 6253.8) are keen to point out that any such definition must be relativized to a specific environment. That is, the essential genes or number of genes that enable autonomous growth and replication depend on the environment, and the environment used in the study at hand is maximally permissive

[5] Schlaepfer and Weber identify three criteria: Thought experiments 1. serve the non-empirical evaluation of some theoretical proposition, 2. appeal to the imagination, and 3. involve counterfactual scenarios. It is easy to see that the first and last criterion are satisfied: The theoretical proposition that humans could evolve in a way that allows for adhesion-based climbing is rejected on the basis of counterfactual scenario in which humans have disproportionally large extremities. However, it is not clear whether the appeal to the imagination is required; after all, the a simple calculation is at the heart of the argument of Labonte et al.

[6] From this it cannot be deduced that Hutchison et al. define 'life' as autonomous growth and replication. Rather, the notion of an essential gene is a technical term that will be explained below.

(i.e., it supplies all required nutrients in abundance).

With MBG and the motivation in place, let us now take a closer look at JCVI-syn3.0 and the method of Hutchison et al. The general strategy for finding MBG is to take the bacterium with the smallest genome and then to reduce its size whilst retaining the bacterium's autonomous growth and replication, and, for pragmatic reasons, a standard (or elevated) growth rate. Historically, the model organism in question is *Mycoplasma genitalium* with a 580-kilobase pair genome and 475 genes (see Fraser et al. 1995). Now, JCVI-syn3.0 is a cell "that is controlled by a 531-kilobase pair synthetic genome [and 473 genes which] is substantially smaller than that of *M. genitalium*, and its doubling rate is about five times as fast" (Hutchison et al. 2016: 6253.1f.).

To better appreciate this result, it is important to take a look at how Hutchison et al. arrived at JCVI-syn3.0 for even though this new cell is smaller than *M. genitalium*, the mere reduction in genes (minus two) might not be considered to be substantial. Hutchison et al. used the *Mycoplasma mycoides* JCVI-syn1.0 genome as basis of their minimization. JCVI-syn1.0 is a synthetic variant of the *M. mycoides* genome, has a size of 1080 kilobase pairs and 901 genes, and was designed by Daniel Gibson et al. (2010) at the same laboratory. Notwithstanding the larger size of *M. mycoides*, it was chosen over *M. genitalium* due to its much faster growth rate. So JCVI-syn3.0's genome is interesting for two complimentary reasons: It is half the size of JCVI-syn1.0 but yields the same growth rate, and it is about the same size as *M. genitalium* but enables a highly elevated growth rate.

In order to minimize JCVI-syn1.0, its genes were grouped into three categories: Essential, nonessential, and quasi-essential genes. The last category is a novelty and comprises genes "that are needed for robust growth, though not absolutely required" (Hutchison et al. 2016: 6253.1) and was critical in the development of JCVI-syn3.0 as detailed below. This is interesting from a modal perspective since there seem to be at least two different kinds of necessity in play, the latter of which admits itself for grades (to wit, quasi-essential genes "spanned a continuum of growth impairment, varying from minimal to severe" Hutchison et al. 2016: 6253.3).

An additional question is whether an essential or necessary gene is an epistemic or metaphysical notion. In other words: When Hutchison et al. talk of essential genes, do (respectively should) they intend to say something about the fundamental nature of (bacterial) genomes, or are they simply employing a heuristic in order to cut down the bacterium's number of genes? Unsurprisingly, the answer is 'both'; more precisely,

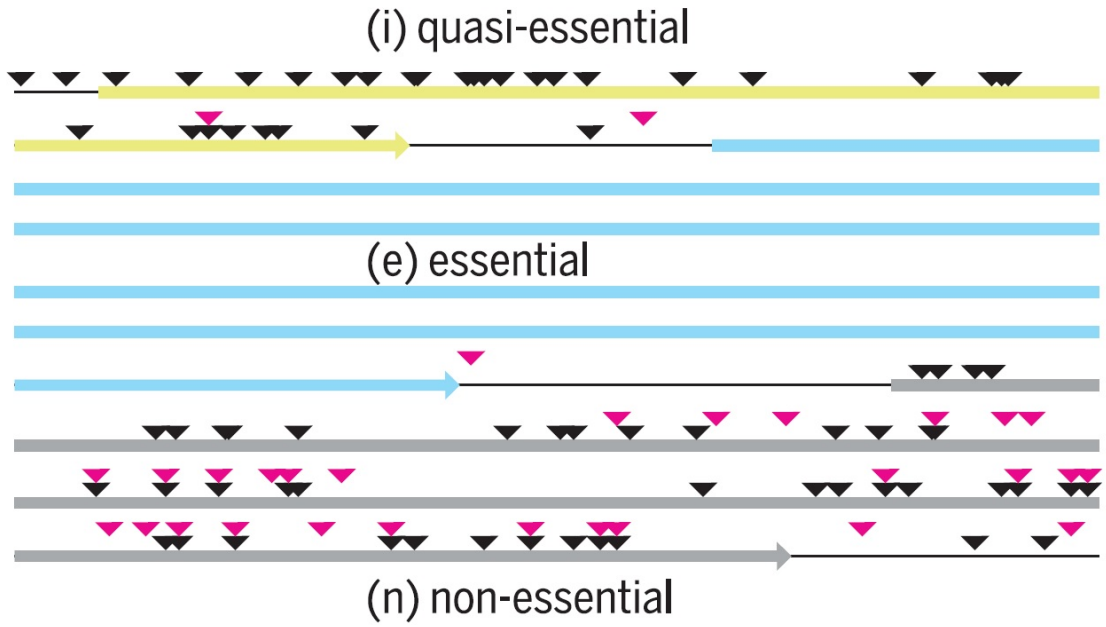


Figure 1.5
Classification of gene essentiality by Tn5 mutagenesis (Hutchison et al. 2016: 6353.4). This image indicates the Tn5 inserts at the genes *MMSYN1_0128* (lime), *MMSYN1_0129* (blue), *MMSYN1_0130* (gray) of JCVI-syn1.0 in the P0 (black triangles) and P4 (magenta triangles) dataset.

I submit that way the notion is employed in their paper is an operationalization of a metaphysical notion. To see this, consider first the crucial role of Tn5 mutagenesis (a kind of transposon mutagenesis) in order to identify essential, nonessential and quasi-essential genes. The following process was employed (Hutchison et al. 2016: 6253.3): A JVCIsyn1.0 cell was exposed to a single Tn5 insertion and then grown into a colony. This was repeated 80'000 times. These colonies were then pooled. Analyzing a sample revealed 30'000 unique mutations (dataset P0). The sample was then grown for 40 generations, revealing 14'000 unique mutation (dataset P4). This then gives rise to the following classification schema of gene essentiality:

> Genes fell into three major groups: 1. Genes that were not hit at all, or that were sparsely hit in the terminal 20% of the 3'-end or the first few bases of the 5'-end, were classified as essential [...] 2. Genes that were hit frequently by both P0 and P4 insertions were classified as nonessential [...] 3. Genes hit primarily by P0 insertions but not P4 insertions were classified

> as quasi-essential, the deletion of which would cause growth impairments [...] (Hutchison et al. 2016: 6253.3).

See Figure 1.5 for an example. A classification based on Tn5 mutagenesis is a fallible heuristic; this is underscored by the fact that Hutchison et al. (2016: 6353.3) used deletion analysis to confirm their classification, and is also illustrated the existence of redundant genes for essential functions. These pairs of genes can be characterized as follows: For some essential or quasi-essential function f, there are two genes g, g' each of which is sufficient to cause f; if g is disrupted by Tn5 mutagenesis (or deleted in the deletion analysis), f is still caused by g'. Hence g is classified as nonessential, and similar for g'. But if both g and g' are then left out in the next design-build-test cycle, f is missing and the resulting cell is not viable.

The importance of the explanatory role of biological modalities in the case at hand should be clear. To be maximially explicit, the notion of an essential gene is a modal notion: Instead of 'essential gene', we could say 'necessary gene'. Put differently, the first definition of MBG can be restated as: MBG is a genome such that all its genes are necessary (and perhaps sufficient) for life. Conversely for the second definition: MBG is the smallest genome such that autonomous growth and replication are possible.

1.2.4 Habitability

In a recent paper by the astrobiologist Charles Cockell and a panel of his colleagues (2016), 'habitability' is reviewed. This notion plays a crucial epistemic role in the search for extraterrestrial life: Put roughly, providing criteria for the possibility of life is a heuristic to exclude planetary bodies from the search set and hence increases efficiency by facilitating an appropriate allocation of sparse resources. In what follows, I will spell out in detail the definition of habitability provided by Cockell et al. and make explicit a number of ways in which the modal import of 'habitability' comes into play.

Consider the proposed definition of habitability:

> We define ['habitability'] as the ability of an environment to support the activity of at least one known organism [...] where 'activity' (and thus 'living') is metabolic activity allowing for survival, maintenance, growth, or reproduction (Cockell et al. 2016: 89f.).

This can be restated as follows for some environment E:

E is habitable iff there is a known organism x such that it is possible for x to live in E (1.15)

Cockell et al. take care and effort to discuss and disarm a number of difficulties related to using 'activity' as proxy for 'living'. However, I want to focus on two different aspects of (1.15), namely the notion of a known organism, and what exactly is meant by 'possible' (or 'ability' in the original formulation).

I begin by discussing the former. Cockell et al. do not explicitly say what they mean by a known organism apart from the fact that its use relativizes (1.15) to the current state of knowledge in biology. What can be gathered is that 'known organism' refers to a type and not a token, and that the type in question is not a taxonomic class but rather given by known design principles or biological mechanisms. For example, compare an organism that relies on reduction-oxidation reactions to gain energy with an organism that uses gravitational or radioactive energy; the former is known, the latter not. To see this, consider the rationale for restricting (1.15):

> We do not know whether terrestrial life represents a universal norm [...] However, by constraining habitability to known life, we avoid the term becoming inextricably linked to the problem of defining life [...] or becoming defined by speculative capacities of unknown organisms (Cockell et al. 2016: 89f.).

It is noteworthy that Cockell et al. distinguish between two kinds of modal reasoning to which they attach contrary epistemic evaluations: An epistemically salient kind which is concerned with possible habitats, and a kind which is concerned with possible organisms and deemed epistemically problematic. The implicitly supplied reason is that the former kind is based on actual habitats whereas the latter kind is speculative due to its lack of an actual basis.

Let me now turn to the 'ability' in 'habitability'. Cockell et al. (2016: 94) distinguish between 'instantaneous habitability' and 'continuous habitability': The former is habitability without any constraint on time; the latter is habitability on a geological timescale (i.e., over millions of years). They provide material conditions for both cases. For illustration, consider the four conditions identified for instantaneous habitability (adapted from Cockell et al. 2016: 94):

1. A solvent such as water.

2. Appropriate physicochemical conditions such as temperature.
3. Available energy such as sunlight.
4. The elements CHNOPS (carbon, hydrogen, nitrogen, oxygen, phosphorus, sulfur).

If we plug these conditions into (1.15), we get:

E is (instantaneous) habitable iff E satisfies 1. to 4. for some known organism (1.16)

A couple of remarks are in order. First, 'habitability' is certainly a biological notion, however, the kind of biological possibility in (1.15) seems to be reducible, at least partially, to non-biological terms or explanations. Second, the kind of biological possibility in (1.15) seems to be more fundamental than, say, an animal's biological possibility to grow allometric sticky footpads. Finally, with respect to conditions 1. to 4., 1. to 3. can be satisfied in a number of different ways whereas 4. is non-negotiable.

1.3 Desiderata

The above discussion of the four cases yields a number of desiderata for a theory of biological modalities. In this section, I will compile a list of desiderata and amend it with more general considerations. This list will serve as rough guideline for subsequent chapters. I will then explore on a qualitative level whether philosophy of biology provides (some of) the resources to build a theory of biological modalities.

1.3.1 What is needed

Two kinds of desiderata need to be distinguished. The first kind pertains to the content of a theory of biological modalities; by contrast, the second kind concerns what such a theory can be used for, broadly construed.

With respect to the content of a theory of biological modalities, there a three main questions that I am interested in answering:

How are biological modalities defined? (D1)
What is the relationship between biological and other modalities? (D2)
Are there different grades of biological modalities? (D3)

Recall that the notion of a biological modality is an umbrella term for a range of rather diverse notions and phenomena. Here I limit myself to biological possibility, biological necessity, and biological counterfactuals. So items (D1)–(D3) should be understood as questions about biological possibility, necessity, and counterfactuals. However, for pragmatic considerations that will become apparent later, the main focus of inquiry in chapters 2 and 3 will lie upon biological possibility.

Let me now briefly elaborate on how to parse the items in the list of desiderata. The question (D1) of how biological modalities are defined requires two clarifications. First, this question has descriptive and a normative reading; both readings will be addressed. Second, a semantic concept of definition is assumed. That is, I read the question as asking about the truth conditions of sentences or propositions employing biological modalities. The question (D2) about the relationship between biological and other modalities requires as answer an ordering of or a principle for ordering these modalities. For example, does biological possibility imply physical possibility? Finally, the question (D3) about different grades of biological possibility is aimed at elucidating whether or not there is a monolithic notion of (say) biological possibility. In short, the three questions could be synthesized into the following question: What is the logic of biological modalities? Clarificatory work on all three questions will be undertaken in chapter 2.

I will now turn to the desiderata with respect to the operative range of a theory of biological modalities. Such a theory should be:

Applicable to biological practice, (D4)

conducive to clarifying modal notions in biology, and (D5)

embedded in a well-understood and unified (formal) framework. (D6)

Why (D4)–(D6)? The most important (D4) is to ensure that biological practice is taken seriously. That is, a theory of biological modalities should informed by biological practice. Such a theory has therefore a strong epistemic (or pragmatic) component. (D5) provides a broader target for the theory than formulated in the questions above. Finally, (D6) is to ensure that the wealth of (formal) frameworks is taken into consideration in order to prevent idiosyncrasy and having to reinvent the wheel.

To sum up, my goal is to provide an account or logic of biological modalities that helps to better understand biological practice.

1.3.2 What philosophy of biology has to offer

In philosophy of biology, publications about biological modalities (in the sense of subsection 1.1) either engage with biological modalities directly, indirectly or not at all. In what follows, I will spell out these three categories in more detail, populate them with examples whenever possible, and determine their value with respect to answering the main questions formulated above.

The first category comprises explicit definitions of biological modalities. To my knowledge and based on section 1.1, the only such definition is due to Daniel Dennett (1995) and will be discussed in detail chapter 3. In a nutshell, he defines biological possibility as a relation between genomes in the logical space of all genomes. While Dennett's definition has many shortcomings, it will nevertheless serve as stepping stone for the construction of a number of modal logics of biological modalities in chapters 4–7.

The second category comprises explicit definitions of modal notions in biology. While items in this category cannot help us in answering the three main questions formulated above, they do help in better estimating the operative range of a theory of biological modalities. For illustration, consider the following examples taken from three distinct debates:

1. Arno Wouters (2003, 2007) argues that there is an important type of functional explanation in biology which he calls 'design explanation' (see Wouters 2005 for an overview of the function debate). Design explanations employ a notion of biological function as biological advantage. Here the function of a trait "are the abilities resulting from that trait, due to which organisms possessing it have better life chances than similar organisms lacking it, or in which this trait is replaced by another" (Wouters 2003: 643). Crucial for the discussion at hand is the observation that the notion of function as biological advantage relies on counterfactual comparison, namely the comparison between actual and non-actual organisms.[7] For example, consider the gecko (or other animals discussed in subsection 1.2.2): Its sticky footpads have the biological function as advantage to climb smooth vertical surfaces since the ability to climb smooth vertical surfaces opens up new habitats and hence increases their life chances over similar animals without sticky footpads. Two additional remarks are in order. First specifying the appropriate non-actual

[7] I have argued elswhere (see my Huber 2013) that counterfactual comparison also plays a crucial role in other popular notions of biologicla function based on Bas van Fraassen's (1973) work on contrast classes.

organisms is a non-trivial task. In some cases, the appropriate non-actual organisms are biologically possible; in other cases, the appropriate non-actual organisms are biologically impossible. This difficulty is related to the following challenge put forward by Ruth Millikan (1993): Counterfactual situations in which organisms lack a certain trait are indeterminate. Put differently, the lack of (say) sticky footpads can be realized in many different ways. Therefore, she concludes, counterfactual comparisons lack definite truth values. Wouters replies that Millikan conflates two notions of biological function, namely function as biological role which is not contrastive and function as biological advantage which is contrastive. Second, even assuming that this reply is convincing, the challenge of providing explicit truth conditions for counterfactual comparisons or so-called 'functional counterfactuals' (Wouters 1999: 138–150) still remains unanswered.

2. Marcel Weber (forthcoming) argues against the causal parity thesis (i.e., the claim that there are no privileged causes such as genes with respect to the development of organisms) by introducing a new kind of counterfactual. Such a counterfactual is special in that its antecedent is brought about by a biologically normal intervention.[8] Biologically normal interventions are defined as interventions in the sense of Woodward (2003) supplemented with two additional constraints, namely that "they 1. could be brought about by natural biological processes and 2. don't kill the organism considered" (Weber forthcoming: 32). However, similar to the example of functional counterfactuals, an explicit semantics of the counterfactuals in question is not provided.

3. Oliver Lean (2016) proposes a definition of arbitrariness in molecular biology. Following Ulrich Stegmann (2004), he takes arbitrariness to apply to the relations between biological entities. Stegman defines arbitrary relations in terms of chemical laws, namely as relations that are not chemically necessary. By contrast, Lean defines arbitrary relations in terms of biological intermediates. Here a biological intermediate is an evolvable biological structure such as nucleic acid polymers or proteins that causally mediates (in the sense of Pearl 2001) between the relata. For example, consider the relation between cytoplasmic lactose and the lactase genes, the former of which causes the expression of the latter. Lean argues that this relation is arbitrary since it is causally mediated by the lactase repressor (which is an evolable biological structure): Cytoplasmic lactose causes a conformational change

[8] I do not use Weber's term of 'biological counterfactual' in order to avoid terminological ambiguities especially with respect to chapter 9.

in the lactase repressor which in turn causes the loss of the lactase repressor to bind to the lactase genes thus enabling their expression.

I take it that all three examples could benefit from a theory of biological modalities; I will get back to some of them in part III.

The last category comprises implicit definitions of biological modalities or modal notions. For the purpose at hand, publications in this category are not relevant with the exception of providing negative examples of what can go wrong such as the implicit assumption to define biological modalities in terms of laws. For illustration, consider Bence Nanay's (2010) modal theory of biological function. Here biological function is defined in terms of counterfactuals and relies on the standard semantics for counterfactual conditionals due to David Lewis (1979). Put roughly, these semantics are based on a similarity ordering measuring the extent to which laws of nature have been violated. In chapter 2, I will reject the implicit definition of biological modalities in terms of laws. In addition, in chapter 9, I will provide a semantics of biological counterfactuals that is not grounded in laws. For a detailed critique of the modal theory of function, see my Leahy and Huber (2014).

To sum up, philosophy of biology has not much to offer in terms of direct answers to the three main questions stipulated in subsection 1.3.1. However, it provides some insight into how to (not) formulate an account of biological modalities and where it could be usefully applied.

1.4 Summary

I argue that there is a tension between (1) the lack of philosophical interest in biological modalities and (2) the important explanatory role biological modalities play in biological practice. The first claim is supported by a quantitative analysis of major academic databases and a qualitative survey of the philosophical literature. I defend the second claim by four 'arguments from case study' pertaining to coiled ammonoid shell form, sticky footpads and maximum body size, the minimal bacterial genome and essential genes, and the habitability of exoplanets. I propose that a theory or logic of biological modalities could fill the epistemic lacunae between (1) and (2) by providing truth-conditions for biological modalities, shedding light on the relationship between biological and other modalities, and spelling out how biological modalities can be graded.

2. Clarifications

In this chapter, I will provide two clarifications with respect to biological modalities. First, in section 2.1, I reject the intuitive idea that biological modalities are best defined in terms of biological laws. Second, in section 2.2, I will disambiguate and spell out three ways in which biological modalities can be graded.

2.1 Possibility as consistency with laws

What is logically respectively physically possible?[1] An intuitive answer is: Well, whatever does not violate logical respectively physical laws. For illustration, consider an example due to Daniel Dennett (1995: 105) which trades on the difference between two fictional characters called Superman and Duperman: Superman can fly faster than the speed of light whereas Duperman can fly faster than the speed of light without moving anywhere. Superman is not physically possible since flying faster than the speed of light violates the laws of physics; Superman is logically possible since flying faster than the speed of light does not violate the laws of logic. By contrast, Duperman is neither physically nor logically possible since flying faster than the speed of light without moving anywhere violates the laws of logic.[2] So let me introduce a third fictional character, call him Hyperman, and stipulate that he does not age. Hyperman is logically and physically possible (see Knell and Weber 2009), but is he biologically possible? It is tempting to

[1] In this section, I focus on defining possibility; due to the interdefinability between possibility and necessity, all results also apply to necessity.

[2] The example presupposes that if Duperman flies faster than the speed of light, he moves somewhere. This is contested in the Futurama episode "A Clone of My Own" where the Planet Express spacecraft's dark matter engine is explained to enable the spacecraft's faster-than-light flight by moving the universe instead of the spacecraft. If Duperman is granted to make use of a similar mechanism, he is logically possible. In order to provide an example which adequately captures the difference between physical and logical possibility, consider thus Ultraman who can fly faster than the speed of light without flying faster than the speed of light. Ultraman is not only physically impossible, he is also logically impossible since the logical law of non-contradiction is violated.

answer: If a lack of senescence violates the laws of biology, Hyperman is biologically possible; otherwise he is not.

In this section, I will argue that this intuitive answer does not make the cut. More precisely, in subsection 2.1.1, I will show that it is unproblematic to define logical possibility as non-violation of logical laws. I will then in subsection 2.1.2 make explicit a number of problems when defining physical possibility as non-violation of physical laws. Finally, in subsection 2.1.3, I will reject the idea to define biological possibility as non-violation of biological laws.

2.1.1 Laws of logic

Here is the standard way to spell out the idea of defining logical possibility as non-violation of logical laws (e.g., Robertson and Atkins 2013, Vaidya 2015):

Definition 2.1 (Logical possibility)
A sentence ϕ is logically possible if and only if ϕ is consistent with the laws of logic.

Definition 2.1 is phrased in terms of sentences; alternatively, it can also be stated in terms of facts or states of affairs, along the following lines: That a state of affairs obtains is logically possible if and only if it is consistent with the laws of logic. However, a requirement of getting this reformulation off the ground is to make explicit how the logical notion of consistency can be applied to non-abstract entities. Since I have no desire in doing so, I will stick with definition 2.1 as is.

Definition 2.1 requires further clarification. An initial complication concerns its definiendum and pertains to the distinction between possibility de dicto and possibility de re. From a semantic perspective, the former attributes possibility to a sentence; the latter attributes possibility to an individual. Consider again the example of Superman and his ability to fly faster than the speed of light. There are two salient interpretations, the first of which is de dicto and the second of which is de re:

1. It is logically possible that Superman flies faster than the speed of light.
2. Superman is such that it is logically possible for him to fly faster than the speed of light.

However, the distinction between possibility de dicto and possibility de re can also be drawn on purely syntactic (and hence less contagious) grounds. This requires quantified

first-order modal logic (e.g., see Girle 2003: 48–94). For the purpose at hand, we can get away with a cursory glance at this logic. In order to obtain the quantified modal language, simply extend the classical first order language with the unary non-binding operator '$\Diamond$' which is interpreted as logical possibility. Let 'FTL' be a unary predicate for faster-than-light flight and let 'superman' be an individual constant denoting Superman:

$$\Diamond\exists x(x = \text{superman} \wedge \text{FTL}(x)) \tag{2.1}$$

$$\exists x(x = \text{superman} \wedge \Diamond\text{FTL}(x)) \tag{2.2}$$

From a syntactic perspective, the difference between a sentence de dicto and a sentence de re is simply a matter of what is in the scope of the $\Diamond$-modality: A sentence ψ containing a modal operator is de dicto if and only if all modal operators in ψ have no unbound individual variables in their scope; otherwise ψ is de re (Hughes and Cresswell 1968: 184). Hence (2.1) is de dicto because the diamond-operator has the closed formula

$$\exists x(x = \text{superman} \wedge \text{FTL}(x)) \tag{2.3}$$

within its scope; by contrast, (2.2) is de re because the $\Diamond$-modality has the unbound individual variable x within its scope. So the logical possibility in play in the definiendum of definition 2.1 is logical possibility de dicto since ϕ is a sentence and sentences are closed formulas.

In what follows, I will by default refer to de dicto possibility. There are three reasons for this. First, much of what I have to say about de dicto possibility also applies to de re possibility; I will explicitly point out interesting cases of divergence. Second, my formal tool of choice in chapters 4–7 will be propositional modal logic. In this formal framework, the distinction between de dicto and de re modalities cannot be drawn. This is a blind spot, but it is well-justified: Even though quantified modal first-order logic is more expressive than propositional modal logic, it lacks many of the latter's nice features. Finally, I will address the distinction between de dicto and de re in a biological context in chapter 7.

Let us now turn to the definiens of definition 2.1. Two clarifications are in order:

1. The notion of logic is ambiguous between different logics, for example classical propositional logic, propositional para-consistent logic, propositional modal logic, and so on. For simplicity, I will opt for classical propositional logic (CPL) in what follows.

2. From a syntactic perspective, how to spell out the notion of a law of CPL depends on what proof system one prefers. In an axiomatic system, the laws of CPL are simply the axioms of CPL. Then a sentence ϕ is consistent with the laws of CPL if and only if a contradiction cannot be deduced from the union of ϕ and the axioms of CPL via modus ponens. In an system of natural deduction, the laws of CPL are the inference rules. Then ϕ is consistent with the laws of CLP if and only if a contradiction cannot be deduced from ϕ via the inference rules. And so on for other proof systems. Alternatively, from a semantic perspective, ϕ is consistent with the laws of CLP if and only if the truth table of ϕ has at least one true row. To wit, things get more complicated when considering more expressive logics than CPL, but task of making explicit the notion of the corresponding logical laws remains similar.

The notion of logical possibility defined along these lines is ubiquitous in many philosophical debates albeit it does not go uncontested (e.g., see Seddon 1972).

2.1.2 Natural laws

Consider now the standard way to spell out the idea of defining physical possibility as non-violation of physical laws; here definition 2.1 is taken as a template:

Definition 2.2 (Physical possibility)
A sentence ϕ is physically possible if and only if ϕ is consistent with the laws of physics.

Instances or variants of definition 2.2 are quite common (e.g., see Kment 2012). Definition 2.2 is more problematic than definition 2.1 due to the contentious issue of explicating physical laws. There are many rivaling (families of) accounts of physical laws (see Psillos 2003; Carroll 2010). I remain agnostic with respect to the nature of physical laws. However, I want to submit the following observation: Plugging popular accounts of physical laws into definition 2.2 either reduces it to definition 2.1 or renders it circular. I will discuss the horns of this dilemma in turn.

The first horn pertains to anti-realist accounts of physical laws. These accounts maintain that physical laws do not exist. Here a prominent example is Bas van Fraassen (1989)

explanatory project	explanandum	explanans
ML	modalities	laws
LM	laws	modalities

Table 2.1
Two explanatory directions for modalities and laws: Explaining modalities in terms of laws (ML) versus explaining laws in terms of modalities (LM).

who argues that physical laws fail to meet important criteria of explanatory adequacy.[3] Plugging an anti-realist account into definition 2.2 yields: A sentence ϕ is physically possible if and only if ϕ is consistent with the empty set. But ϕ is trivially consistent with the empty set if ϕ is not a contradiction. Therefore, ϕ is physically possible if and only if ϕ is not a logical contradiction. So plugging an anti-realist account into definition 2.2 reduces it to definition 2.1. This clearly misses the mark since physical possibility is not logical possibility, or so we assumed.

In order to explicate the second horn, it is helpful to distinguish two distinct yet interrelated explanatory projects which are easily conflated: The first project, call it 'ML', explains modalities in terms of laws whereas the second project, call it 'LM', explains laws in terms of modalities (see Table 2.1). Definitions 2.1 and 2.2 are instances of ML: Logical respectively physical possibility is defined as non-violation of logical respectively physical laws. LM is a subclass of the class of reductive accounts of physical laws. Reductive accounts of physical laws explicate physical laws in lawless (for lack of a better word) terms. The second horn pertains to LM: Plugging an LM-account of physical laws into definition 2.2 renders the definition circular. I propose to distinguish two ways in which this can happen:

1. Physical laws are explicated in terms of primitive modalities. A primitive modality is a modality which is not (weak version) or cannot (strong version) be further explicated. Plugging an explication of physical laws in terms of primitive modalities

[3] "The major criteria concern what I call the problems of inference and identification. The accounts must show that there is a valid inference from what laws there are to what regularities there are in the world. The account must also identify the relevant aspects of the world that constitute or give rise to its laws, if any. Typically these two tasks lead to a dilemma. If laws of nature are identified in terms of some sort of necessity in nature which is simply postulated as fact, then there is no logical reason to think that the inference from lawlike necessity to actuality is valid. (Calling the postulated factor 'necessity' or 'necessitation' does not help.) If on the other hand the semantic account of law statements is so constructed that the inference in question is logically valid, then typically the truth conditions of law statements involve something unidentifiable" (van Fraassen 1993: 411).

into definition 2.2 amounts to an explication of physical possibility in terms of primitive modalities. This can mean one of two things. Either physical possibility is a primitive modality; or physical modality is not primitive itself but a derivative of primitive modalities. The first case is circular because no explication of physical possibility is offered; the same holds for the second case with the complication of a number of intermediate steps.

For example, consider the manipulationist framework of James Woodward (2003). Here a physical law is an invariant generalization; a generalization is said to be invariant if it supports so-called 'same object counterfactuals'. That is, for some object o, "[i]f the value assigned by the variable X to o were to be changed via an intervention (e.g., from $X(o) = 0$ to $X(o) = 1$), then the value assigned by Y to o would change in some way predicted by the generalization" (Woodward 2003: 281). Plugging the manipulationist framework into definition 2.2 yields: A proposition ϕ is physically possible if and only if ϕ is consistent with the generalizations which support same object counterfactuals. But what are the truth conditions of same object counterfactuals? Woodward "fail[s] to provide truth conditions " (Reutlinger 2013) or at most provides "an account of truth conditions [which] is incomplete" (Briggs 2012); hence same object counterfactuals are at least weakly primitive. Plugging the manipulationist framework into definition 2.2 therefore boils down to the statement that physical possibility is a special kind of modality. This is circular or at least non-explanatory in the context of ML.

It is worthwhile to consider an objection to my rejection of the manipulationist framework in the context of ML: It does not matter that same object counterfactuals are weakly primitive because they are not strongly primitive. That is, even if Woodward does not provide truth conditions of same object counterfactuals, such truth conditions can in fact be provided. In response, it is clear that these truth conditions must satisfy a number of constraints in order to be compatible with the manipulationist framework (see Reutlinger 2013: chapter 3). Granting that some truth conditions satisfy these constraints, these truth conditions must in turn be stated in a manner which avoids the circularity charge. This will turn out to be difficult due to the reliance of same object counterfactuals on the notion of an intervention. An intervention is a modal notion because interventions are required to be possible. What kind of possibility is in play here? If it is physical possibility, then the resulting circularity is straightforward (see 2. below for details). Woodward (2003: 128ff.) denies that interventions must be physically possible by providing

a number of examples. It is methodologically awkward to assess these examples since he relies on definition 2.2 to explicate physical possibility; perhaps this is sufficient to underscore the problem of circularity. But let us go a step further. Woodward claims that "an intervention on X with respect to Y will be 'possible' as long as it is logically or conceptually possible for a process meeting the conditions for an intervention on X with respect to Y to occur" (Woodward 2003: 132). However, Alexander Reutlinger (2012) shows that this notion of possibility is too weak and severely hinders any attempt to provide adequate truth conditions of same object counterfactuals. So the onus is (still) on proponents of the objection to demonstrate that same object counterfactuals are weakly primitive.

2. Physical laws are explicated in terms of physical modalities. The resulting problem is straightforward since definition 2.2 attains to explicate physical possibility; explicating physical possibility in terms of physical possibility is circular. For example, take the DTA-account (after Dretske 1977, Tooley 1977 and Armstrong 1983). Its main idea is that a physical law is a second-order relation between universals. More precisely, for universals F, G, if it is a law that Fs are Gs, then a "certain relation, a relation of non-logical or contingent necessitation, holds between F-ness and G-ness" (Armstrong 1983: 85). Let us plug the DTA-account into definition 2.2: A proposition ϕ is physically possible if and only if ϕ is consistent with the non-logical or contingent necessitation relation(s) between the pertinent universals. This resulting definition is circular given two assumptions: First and uncontroversially, physical possibility and physical necessity are interdefinable. And second, non-logical or contingent necessity is or is akin to physical necessity. Since logical and metaphysical necessity are excluded from the start, physical necessity is the only alternative.

The upshot of the discussion of the dilemma is this: In order to get definition 2.2 off the ground, an account of physical laws is required. Such an account must satisfy two constraints: First, it must be a realist account of physical laws in order to block a reduction of physical possibility to logical possibility. Second, it cannot be an LM-account of physical laws on pain of circularity. This is not to show that definition 2.2 is a non-starter for there is at least one account that might fit the profile, namely the best systems account of David Lewis (1973). Here "a contingent generalization is a law of nature if and only if it appears as a theorem (or axiom) in each of the true deductive systems that achieves a best combination of simplicity and strength" (Lewis 1973: 73). So a best system has two properties: First, it is a true deductive system meaning that

the axioms and theorems of the deductive system are true. Second, the trade-off between simplicity and strength is optimal; simplicity and strength cannot both be maximized since adding and axiom increases the strength of a deductive system but decreases its simplicity. Plugging the best systems account into definition 2.2 yields: A proposition ϕ is physically possible if and only if ϕ is consistent with the best true deductive systems. Put differently, ϕ is physically possible if and only if a contradiction cannot be deduced from the union of ϕ and the axioms of the best true deductive system (for each best true deductive system if there are ties between true deductive systems with respect to simplicity and strength). So neither a reduction to definition 2.1 nor circularity is a problem for the best systems account. However, the above discussion is meant to make explicit some of the commitments involved in buying into defining physical possibility as non-violation of physical laws: Important accounts of physical laws are ruled out and one is at the mercy of the best systems account with all its problems (e.g., see Woodward 2014 for a recent discussion).

2.1.3 Biological laws

I will now turn to biological possibility. Let me first make precise the idea of defining biological possibility as non-violation of biological laws:

Definition 2.3 (Biological possibility)
A sentence ϕ is biologically possible if and only if ϕ is consistent with the laws of biology.

Definition 2.3 is an instance of a more general schema (e.g., employed by Robertson and Atkins 2013):

Definition 2.4 (Special science possibility)
For some special science S, ϕ is S-possible if and only if ϕ is consistent with the laws of S.

The difficulties related to plugging popular accounts of physical laws into definition 2.2 can be reiterated with respect to definition 2.3: Most accounts of biological laws cannot be plugged into definition 2.3 on pain of reducing it to definition 2.1 or definition 2.2, or rendering it circular. Let me review which accounts must be excluded on the basis of one of these two problems.

First, consider the problem of reducing biological possibility to logical or physical possibility. This concerns anti-realist accounts of biological laws. There are two variants of this problem related to two species of anti-realism about biological laws:

1. Denying the existence of biological laws reduces biological possibility to logical possibility. For example, John Beatty (2006) argues on the basis of the evolutionary contingency thesis that laws of biology do not exist.[4] Plugging Beatty's account into definition 2.3 yields: A sentence ϕ is biologically possible if and only if ϕ is consistent with the empty set if and only if ϕ is not a logical contradiction. So plugging Beatty's account into definition 2.3 reduces it to definition 2.1.

2. Reducing biological laws to physical laws reduces biological possibility to physical possibility. Of course, there is variety of different kinds of reductionism (see Brigandt and Love 2012 for an overview); here I have the epistemic kind in mind, as exemplified by the so-called 'conservative reductionism' by Christian Sachse (2012). Plugging such an account into definition 2.3 reduces biological possibility to physical possibility: A sentence ϕ is biologically possible if and only if ϕ is consistent with the laws of physics.

   Note that this kind of problem applies more generally to all kinds of reductions of biological laws. For example, consider the reduction of biological laws to mathematical laws. Samir Okasha argues that the Price equation "is simply a mathematical tautology whose truth follows from the definition of the terms" since "nothing is assumed about the nature of the 'entities', their mode of reproduction, the mechanisms of inheritance, the genetic basis of the character, or anything else" (2006: 24).[5]

Let us now turn to the circularity problem. It pertains to realist accounts of biological laws which explicate laws in terms of modalities. This can happen in two ways analogous what was proposed in the previous subsection:

[4] The evolutionary contingency thesis states that all generalizations about biological entities "i. are just mathematical, physical, or chemical generalizations (or deductive consequences of mathematical, physical, or chemical generalizations plus initial conditions), or ii. are distinctively biological, in which case they describe contingent outcomes of evolution" (Beatty 2006: 218) With respect to the second disjunct, note that "to say that biological generalizations are evolutionarily contingent is to say that they are not laws of nature—they do not express any natural necessity; they may be true, but nothing in nature necessitates their truth" (Beatty 2006: 221). That is, the contingency thesis itself is an example of LM and its associated problems.

[5] This example is due to Mauro Dorato (2012) who provides an insightful discussion of reducing biological laws to mathematical laws.

1. Biological laws are explicated in terms of primitive modalities. The most salient example here is again the manipulationist framework which has been applied to biology (see Woodward 2010: 296). Similar considerations as in the previous section apply.

2. Biological laws are explicated in terms of biological modalities. To my knowledge, no such theory has been defended in print. However, a borderline case is Chris Haufe (2013) who argues that biological laws are best understood in terms of necessary chances. Such necessary chances are derived from mathematical laws but claimed to be biological due to their interpretation. So if Haufe's account is plugged into definition 2.3, we get: A sentence ϕ is biologically possible if and only if ϕ is consistent with the (predicted) necessary chances. This resulting definition is circular since the notion of a necessary chance is assumed to be a biological modality.

Given the above discussion, the constraints on an account of biological laws that can be plugged into definition 2.3 are as follows: It must be a realist account of biological laws; and it cannot be a LM-account of biological laws. The only candidate account that fits this bill is the better best systems account of Markus Schrenk (2007) and Jonathan Cohen and Craig Callender (2009). The better best systems account is intended to improve upon the best systems accounts; crucial for the discussion at hand is the desideratum to "allow for laws in the special sciences" (Cohen and Callender 2009: 4). However, similar to the best systems account, the better best systems account faces a host of objections (e.g., see Backmann and Reutlinger 2014).

In short, the strategy of explicating biological possibility in terms of biological laws stands and falls with committing to a specific theory of special science laws. In other words, explicating biological possibility in terms of biological laws is at best a detour and at worst a dead end. This is not to deny that there might be important explicatory relations between modalities, laws and causation:

> A satisfactory definition of scientific law, a satisfactory theory of confirmation or of disposition terms [...], would solve a large part of the problem of counterfactuals. Accordingly, the lack of a solution to this problem implies that we have no adequate treatment of any of these other topics. Conversely, a solution to the problem of counterfactuals would give us the answer to critical questions about law, confirmation, and the meaning of potentiality (Goodman 1947: 113).

However, a different strategy promises more success for the task at hand: In chapter 3, I will argue that biological possibility is best explicated in terms of a relational semantics.

2.2 Grades of possibility

Grading possibilities rests on two implicit assumptions: First, that there are distinct possibilities, and, second, that these possibilities admit to comparison. Here I will be concerned with three distinct ways in which the notion of grades of possibility can be understood:

1. The distinction of different kinds possibility.
2. The distinction of different kinds of biological possibility.
3. The distinction of different possibilities within a given kind of possibility.

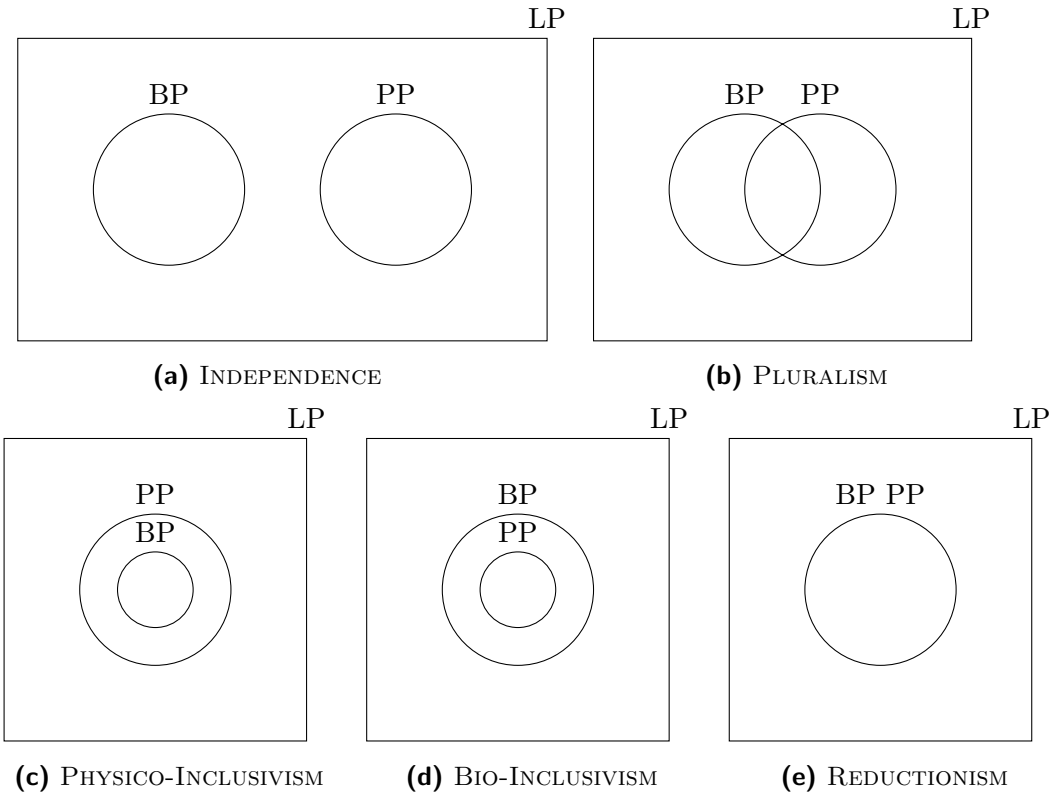
The goal of this section is to provide the conceptual basis for a number of discussions in subsequent chapters.

2.2.1 Inferential relationship

What is the inferential relationship between logical, physical and biological possibility? In order to answer this question, I will assume that logical possibility is given by definition 2.1, namely defined as non-violation of the laws of logic; I remain agnostic with respect to physical and biological possibility. Furthermore, I will assume as uncontroversial two claims: First, everything that is physically or biologically possible is also logically possible; and, second, not everything that is logically possible is also physically or biologically possible. Put differently, logical possibility is a necessary but not suffiecient condition for both biological and physical possibility.

The inferential relationship between physical and biological possibility is then captured by either Independence, Pluralism, Physico-Inclusivism, Bio-Inclusivism or Reductionism as shown in Figure 2.1. Let me explain these positions in more detail and provide some examples of their advocates:

1. Independence is the position that there is no inferential relationship between biological and physical possibility. Somewhat stronger, this could be interpreted as incommensurability in the classical sense (see Kuhn 1962).



(a) Independence **(b)** Pluralism

(c) Physico-Inclusivism **(d)** Bio-Inclusivism **(e)** Reductionism

Figure 2.1

Possible relationships between logical possibility (LP), physical possibility (PP) and biological possibility (BP) represented as Venn diagrams. Independence: BP and PP cannot be compared (for want of joint vocabulary or explanada); nothing BP is PP and vice versa. Pluralism: BP and PP hold their own but can be compared partially; some BP are PP and vice versa, but some BP are not PP and vice versa. Physico-Inclusivism: BP is a special kind of PP; everything BP is also PP, but some PP are not BP. Bio-Inclusivism: PP is a special kind of BP; everything PP is also BP, but some BP are not PP. Reductionism: PP is nothing but BP and vice versa.

2. Physico-Inclusivism holds that physical possibility is a necessary but not sufficient condition for biological possibility. This position is attractive because it is consistent with (or even follows from) two popular ideas: First, the definition of possibility in terms of laws, and, second, the assumption that biological laws (whatever they are) are weaker but not reducible to physical laws. For example, Physico-Inclusivism is explicitly endorsed by Dennett (1995: 107).

3. Bio-Inclusivism claims that biological possibility is a necessary but not sufficient condition for physical possibility. This position is so glaringly incoherent that it has not recently (or ever) been defended in print and does not merit further discussion.

4. Reductionism maintains that biological possibility is nothing but physical possibility; the inferential relation between biological and physical possibility is hence that of (logical) equivalence.

5. Pluralism maintains that biological possibility comes in all of the above flavors (perhaps except Bio-Inclusivism). This yields a case-dependent inferential relation: Sometimes physical possibility (logically) implies biological possibility and sometimes it does not.

An implicit assumption in the above discussion is that biological possibility is a monolithic notion. However, this is not the case; below, I will argue that a range of different notions of biological possibility have to be distinguished. Nevertheless, the inferential relationship between physical possibility and any of these notions is captured by a variant of Independence, Pluralism, Physico-Inclusivism, Bio-Inclusivism or Reductionism.

Before we continue, let me add a disclaimer: Some readers might object to my neglect of other kinds of possibility, especially to the absence of metaphysical possibility. The notion of metaphysical possibility as commonly understood is weaker than logical possibility but stronger than physical possibility (Vaidya 2015). However, an exact definition of this notion is contested and often depends on the particular usage in special debates (e.g., on personal identity, metaphysical grounding, and so on). So while the way the discussion is framed is certainly compatible with adding metaphysical possibility to the mix, this would dramatically increase the complexity of the issues at hand without any apparent epistemic advantages.

2.2.2 Biological possibilities

The notion of biological possibility is an umbrella term for a range of distinct yet related notions. To wit, in section 1.2, I have analyzed examples from astrobiology, biomechanics, ecology, evolutionary biology, molecular biology, synthetic biology, and theoretical morphology. In this section, I will undertake to categorize the encountered (and other) notions of biological possibility. The aim of this categorization is to make plausible the claim that each of these notions requires its own semantics. In order to do so, consider two criteria or factors which I will call Scale and Historicity.

The first factor, Scale, is owed to the observation that wildly different domains of biology rely on notions of biological possibility. One way to distinguish between theses domains is by considering the scale of the biological phenomena under investigation. Scale ranges from molecules over organisms to the biosphere. This heuristic is of course far from perfect since it neglects biological practice and methodology. However, it is simple and a relatively good fit with the self-identified biological domains mentioned above.

Let me now turn to the second factor, Historicity. Daniel Dennett argues that there are at least two notions of biological possibility:

> It seems there might be two kinds or grades of biological impossibility: violation of a biological law of nature (if there are any), and "mere" biohistorical consignment to oblivion. Historical impossibility is simply a matter of opportunities passed up (Dennett 1995: 106).

Even though the way in which this distinction is framed is problematic in light of the previous section, the important take home message is that there is a notion of biological possibility that takes into account evolutionary history whereas there is notion of biological possibility that does not. Call the former 'historical' and the latter 'ahistorical' biological possibility.

Given Scale and Historicity, we can roughly distinguish four (families of) notions of biological possibility, namely historical versus ahistorical biological possibility on a small (molecululer–organism) versus a large (organism–biosphere) scale:

1. HBS is historical biological possibility on a small scale,
2. HBL is historical biological possibility on a large scale,

3. ABS is ahistorical biological possibility on a small scale, and

4. ABL is ahistorical biological possibility on a small scale.

A couple of remarks are in order. First, even though these notions are represented as being discrete, they really are gradual. Second, let me hint at the semantics of these notions: Historical biological possibilities require context sensitive truth conditions whereas ahistorical biological possibilities do not. That is, whether or not something is biological possible given a certain evolutionary history depends, well, on said evolutionary history. For example, recall section 1.2 and David Raup's investigation of ammonoid shell form. Here we can distinguish the question of whether a certain shell form is possible given a particular species of ammonoids from the question of whether a certain shell form is possible given any species of ammonoids. Generally speaking, the more we abstract from the evolutionary history of a particular species, the closer we get to an ahistorical notion of biological possibility. Put differently, ahistorical biological possibility is a minimal notion of biological possibility. Third, the inferential relationship between historical and ahistorical biological possibility is asymmetric: Historical biological possibility implies ahistorical biological possibility, but the inverse does not hold. Finally, the inferential relationship between small-scale and large-scale possibility of the same kind of historicity (that is, the relationship between HBS and HBL, and ABS and ABL respectively) is more complicated.

For illustration, the factors of Scale and Historicity can be compiled into a coordinate system as shown in Figure 2.2; there is a also number of additional examples based on section 1.2.

I take it that these informal remarks are sufficient to establish the existence of distinct yet intelligible notions of biological possibility. In chapters 3 and chapters 5, HBS, HBL, ABS, and ABL will be made more precise. However, let me add two qualifiers: The proposed categorization should be understood as heuristic for making explicit different notions of biological possibility. Second, there certainly are additional factors that would allow for a more fine grained differentiation between notions of biological possibility.

2.2.3 Comparative biological possibility

Can distinct biological possibilities of a certain kind (such as HBS, HBL, etc.) be compared? That is, can it be made intelligible that something is more biologically possible than something else? Given the cases considered in section 1.2, the answer is

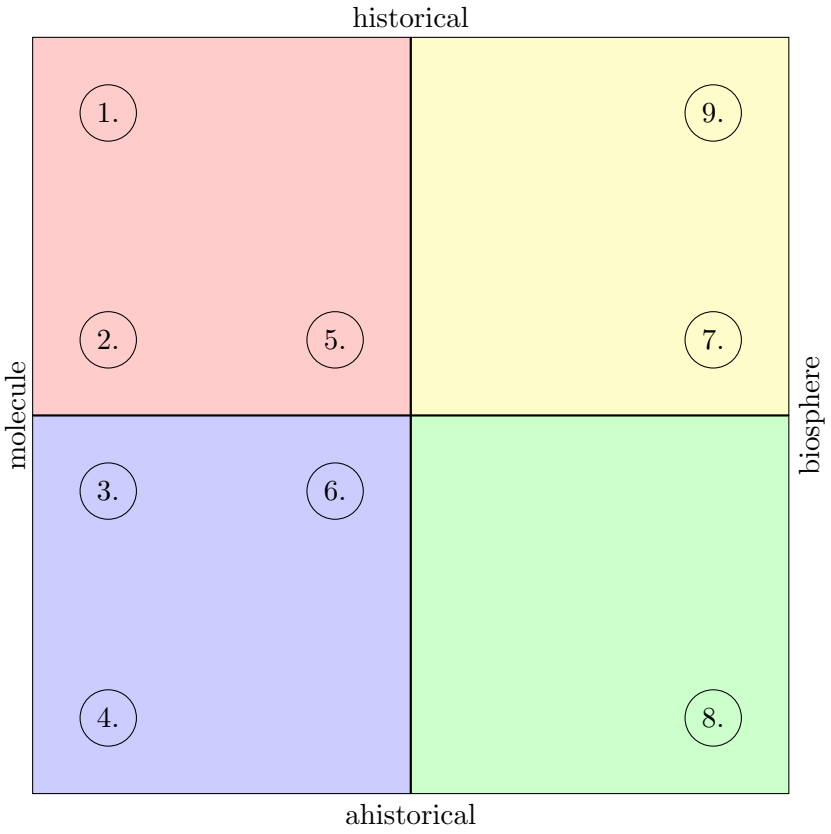


Figure 2.2

Different (families of) notions of biological possibility with HBS (red), HBL (yellow), ABL (green), and ABS (blue) where the x- and y-axis represent Scale and Historicity respectively. The coordinate system is populated with examples related to the paradigmatic cases discussed in chapter 1:

1. Is this gene essential for *M. mycoides* in the sense of Hutchison et al. (2016)?
2. Is this gene essential for bacteria?
3. Is this gene essential for organisms?
4. Is this gene's function essential for organisms?
5. Is overlapping coiled shell form viable for ammonoids?
6. Is overlapping coiled shell form viable?
7. Is this exoplanet habitable in the sense of (1.15)?
8. Is this exoplanet habitable for any kind of organism, known or unknown?
9. Is this exoplanet habitable for a particular kind of known organsim?

yes. To wit, consider three examples (the notions in play here are not always biological possibility proper, but the relevant connections should be apparent):

1. Within the morphospace of coiled ammonoid shell form (that is, within the logical space of such shell form, see subsection 1.2.1), non-overlapping shell form is more biologically possible than overlapping shell form.

2. A quasi-essential gene is a gene whose disruption decreases the growth rate of a cell to decrease (more technically, a quasi-essential gene has Tn5 inserts in the P0 but not the P4 dataset, see subsection 1.2.3). The growth impairment can vary "from minimal to severe" (Hutchison et al. 2016: 6253.3). Therefore, quasi-essential genes can be ordered according to the severity of the growth reduction caused by their disruption. For example, the more severe the growth impairment, the higher the score of the disrupted quasi-essential gene.

3. Environments such as planets can be ordered by their habitability (that is, by their similarity to habitats of known organisms, see subsection 1.2.4). For example, the Habitable Exoplanets Catalog (see phl.upr.edu) provides two such orderings (one conservative and one optimistic) of planets based on the so-called Earth Similarity Index (or ESI in short, see Schulze-Makuch et al. 2011).[6]

So within a given grade of biological possibility B, we can ask whether something is more B-possible than something else. More generally, for the range of B-possibilities $b, b', b'', \ldots$, is there an ordering that can be imposed? Put roughly, there are at least four ways to do say, namely by stipulating that 1. b is more easy to bring about than b', 2. there are more b than b', 3. there are more ways to bring about b than b', and b is more probable than b'. I will provide implementations of all interpretations in chapter 6 and also discuss their respective advantages and disadvantages.

2.3 Summary

I offer two main of clarifications of how (not) to think about biological modalities. First, I argue that defining biological possibility as non-violation of biological laws is problematic since it requires a commitment to both realism about biological laws and the better best

[6] ESI is a statistical measure based on a planet's stellar flux, radius, and other parameters. Note that Schulze-Makuch et al. (2011) also propose the Planetary Habitability Index (PHI); PHI requires more observational data than ESI but is very close in spirit to the material conditions of instantaneous habitability as presented in susection 1.2.4.

systems account of special science laws; otherwise biological possibility is reduced to physical or logical possibility, or its definition is rendered circular. Second, I examine three ideas regarding the grading of (biological) possibility, namely (1) the distinction between kinds of possibility such as logical, physical and biological possibility and (2) between subkinds of biological possibility which roughly map to the scale of biological phenomena under investigation and come in historical or ahistorical flavors, and (3) the observation that some subkinds of biological possibility are comparative.

3. Dennett on biological possibility

Daniel Dennett offers an explicit albeit incomplete definition of biological possibility stating that "x is biologically possible if and only if x is an instantiation of an accessible genome or a feature of its phenotypic products" (1995: 118). The lynchpin of his definition is the Library of Mendel which can be roughly characterized as "the logical space of all genomes" (1995: 123). The goal of this chapter is to show how Dennett's definition can be used as a stepping stone towards a theory of biological modalities.

I will proceed as follows. In section 3.1, a number of technical notions will be introduced. Some context for the Library of Mendel will be provided in section 3.2. In section 3.3, I will unpack and improve upon Dennett's definition by restating the Library of Mendel as relational structure, and I will discuss the advantages and problems of the resulting relational semantics. In section 3.4, I will argue that the most pressing problem can be addressed by interpreting the accessibility relation in the Library of Mendel as solution to a string editing problem.

3.1 Preliminaries

In this section, two (clusters of) technical notions will be introduced, namely relational structures in subsection 3.1.1, and alphabets, strings and languages in subsection 3.1.2. Readers familiar with these notions can go directly to section 3.2.

3.1.1 Relational structures

A relational structure is a set plus a binary relation on that set. Relational structures are ubiquitous both in everyday life and in the sciences. For example, the table of the Swiss Super League (Switzerland's top football league for non-sports fans) is a relational

structure: The set consists of football teams such as FC Basel 1893; the relation on that set is a partial order interpreted as one team having more points than another (or as having a better goal difference in case of a tie). There are many other examples of relational structures of varying complexity, for example the natural numbers, Bayesian networks, biological mechanisms, and so on. Formally, we define relational structures as follows:

Definition 3.1 (Relational structure)
A relational structure is a tuple $\langle D, R\rangle$ where the domain D is a non-empty set and $R \subseteq D \times D$.

I will write dRd' in order to abbreviate $\langle d, d'\rangle \in R$ where $d, d' \in D$.

Relational structures are important because they give rise to relational semantics (or Kripke semantics, after Kripke 1959, 1963). In a nutshell, relational semantics define the truth of certain sentences in terms of the relation(s) between elements of a set. The most widespread application of this idea in philosophy is the definition of the truth conditions of possibility in terms of the relations between possible worlds: $\Diamond\phi$ is true at some world w if and only if there is a world w' such that w has access to w' and ϕ is true at w'; the relational structure underlying these semantics is the set of possible worlds plus the accessibility relation. Historically, the invention of relational semantics "turned modal logic from a rather esoteric branch of syntax manipulation into an concrete and intuitively compelling field" (Blackburn et al. 2001: x). Relational semantics and modal logics will be formally introduced in chapter 5.

3.1.2 Alphabets, strings and languages

Put simply, an alphabet consists of some symbols; a string over an alphabet is any sequence of symbols built from said alphabet; and a language is a collection of strings. However, it is important to stress the technical nature of these notions: They are borrowed from bioinformatics (e.g., Gusfield 1997: 2ff.) and computer science (e.g., Hopcroft et al. 2007: 29ff.) and hence bear little or no resemblance to their use in other scientific contexts. For example, consider the language of English. In many contexts, English would be defined via its syntax and semantics. Not in this context: English simply consists of those strings over the Roman alphabet that are collected in (say) the Oxford Dictionary, irrespective of grammar and meaning. The formal perspective on alphabets,

strings and languages offered in what follows should hence be understood as nothing more but a tool for reasoning about (the manipulation of) sequences of symbols. Let us start off by defining alphabets and strings:

Definition 3.2 (Alphabet)
An alphabet Ω is a non-empty and finite set of symbols.

Definition 3.3 (String)
A string s over Ω is a sequence of elements of Ω.

Ω will be used as meta-variable for any alphabet; token alphabets are indicated by subscripts. Floor corners will be used in order to refer to a token symbol of an alphabet. I will use s with or without subscript as meta-variable for a string over any alphabet. Other lowercase letters such as $b, g, t, \ldots$ with or without subscripts will be used as variables for strings over specific alphabets. The value of such a (meta-)variable, namely a string, is indicated by ceiling corners (both floor and ceiling corners are dropped when there is no risk of confusion). Some examples of alphabets include $\Omega_{\text{Small}} = \{\text{a}, \text{b}\}$, $\Omega_{\text{Suits}} = \{\clubsuit, \diamond, \heartsuit, \spadesuit\}$ and Ω_{Big} = Roman alphabet. The symbol $\lfloor \text{a} \rfloor$ belongs to both Ω_{Small} and Ω_{Big}. $\lceil \text{a} \rceil$ is a string over Ω_{Small} and Ω_{Big}, $\lceil \text{cat} \rceil$ and $\lceil \text{oknwefwebs} \rceil$ are strings over Ω_{Big}.

Some auxiliary notions are required in order to define string concatenation, that is the combination of strings to build a new string:

Definition 3.4 (String length)
The length $|s|$ of a string s denotes the number of positions of s.

Definition 3.5 (Empty string)
The empty string λ is any string s such that $|s| = 0$.

Definition 3.6 (Symbol position)
For $n \in \mathbb{N}_1$, $s(n)$ denotes the symbol at the n-th position of s.

With definitions 3.2–3.8 at hand, string concatenation can be defined:

Definition 3.7 (String concatenation)
Let s, s' be strings over an alphabet Ω. The concatenation $s \oplus s'$ denotes the string that is formed by joining s and s' at $s(|s|)$ and $s'(1)$; if $s' = \lambda$, then $s \oplus s' = s$.

The notion of a substring will be useful:

Definition 3.8 (Substring)
For $1 \leq i, j \leq |s|$, a substring $s[i, j]$ of a string s is a string starting at $s(i)$ and ending at $s(j)$.

For illustration, consider a toy alphabet $\Omega_{\text{Toy}} = \{\text{a}, \text{e}, \text{g}, \text{n}, \text{v}\}$ and two strings over Ω_{Toy}, namely $t = \lceil\text{geneva}\rceil$ and $t' = \lceil\text{gene}\rceil$. The length of these strings is $|t| = 6$ and $|t'| = 4$ respectively. $t(1) = \lfloor\text{g}\rfloor$, $t(2) = \lfloor\text{e}\rfloor$, $t(3) = \lfloor\text{n}\rfloor$, and so on. $t' = \lceil\text{gene}\rceil = t[1, 4]$ and $t[1, |t|] = t$ are substrings of t. $t \oplus t' = \lceil\text{genevagene}\rceil$ is the concatenation of t and t'.

In order to define languages, two additional auxiliary notions are needed:

Definition 3.9 (Alphabet exponentiation)
For an alphabet Ω, a string s over Ω and $n \in \mathbb{N}_0$, $\Omega^n = \{s : |s| = n\}$.

Definition 3.10 (Kleene closure)
The Kleene closure of an alphabet Ω is $\Omega^* = \bigcup_{n \in \mathbb{N}_0} \Omega^n$.

An alphabet to the n-th power is exactly the set of strings over the alphabet with a length of n positions. The Kleene closure of an alphabet is the union of all of the alphabet's exponentiations. Put differently, the Kleene closure of an alphabet is the set of all strings over the alphabet that can be built via concatenation. For example, $\Omega^0_{\text{Small}} = \{\lambda\}$, $\Omega^1_{\text{Small}} = \{\text{a}, \text{b}\}$, $\Omega^2_{\text{Small}} = \{\text{aa}, \text{ab}, \text{ba}, \text{bb}\}$, and so on. Here the Kleene closure is $\Omega^*_{\text{Small}} = \{\lambda, \text{a}, \text{b}, \text{aa}, \text{ab}, \text{ba}, \text{bb}, \text{aaa}, \dots\}$.

Based on definitions 3.2–3.10, languages can be defined:

Definition 3.11 (Language)
$\Sigma \subseteq \Omega^*$ is a language.

Σ will be used as meta-variable for any language; token languages are indicated by subscripts. For example, all words on this page are a language over the set of symbols

used on this page. Note that since the Kleene closure of an alphabet is countably infinite, some languages are countably infinite.

3.2 Context

In this section, I discuss a creative predecessors of the Library of Mendel, namely Jorge Luis Borges' (1998) Library of Babel.[1] This provides the context for the presentation of the Library of Mendel in section 3.3 and anticipates some challenges discussed in section 3.3.4.

The Library of Mendel is an adaption of Jorge Luis Borges' (1998) short story "The Library of Babel". The setting of this story is a peculiar library:

> The universe (which others call the Library) is composed of an indefinite, perhaps infinite number of hexagonal galleries. In the center of each gallery is a ventilation shaft, bounded by a low railing. From any hexagon one can see the floors above and below — one after another, endlessly. The arrangement of the galleries is always the same: Twenty bookshelves, five to each side, line four of the hexagon's six sides; the height of the bookshelves, floor to ceiling, is hardly greater than the height of a normal librarian. [...] Each wall of each hexagon is furnished with five bookshelves; each bookshelf holds thirty-two books identical in format; each book contains four hundred ten pages; each page, forty lines; each line, approximately eighty black letters. [...] There are twenty-five orthographic symbols [namely] the space, the period, the comma, and the twenty-two letters of the alphabet (Borges 1998: 112ff.).

Dennett (1995: 107–111) uses an interpretation of the Library of Babel as template for the Library of Mendel. Central to his interpretation is the observation that the Library of Babel is, in a sense, the logical space of all books. To elucidate this observation, it is instructive to make the Library of Babel more precise by defining its alphabet, books and language by means of the tools of the previous section.

Let us start with the alphabet:

[1] A second source of inspiration for Dennett's Library of Mendel is Richard Dawkins' (1986) so-called 'Biomorph Land' which I will skip here for brevity.

Definition 3.12 (Alphabet of the Library of Babel)
The alphabet of the Library of Babel Ω_{B} contains "the space, the period, the comma, and the twenty-two letters of the alphabet" (Borges 1998: 114).

Exactly which twenty-two letters Borges has in mind is not clear and does not matter for the purpose of this section; Dennet assumes that the alphabet of the Library of Babel contains "the upper- and lowercase letters of English and other European languages, plus the blank and punctuation marks" (1995: 108).

Definition 3.13 (Books in the Library of Babel)
A book b in the Libary of Babel is a string s over Ω_{B} such that $|s| = 410$ (pages) $\times$ 40 (lines per page) $\times$ 80 (symbols per line) $= 1.312 \times 10^6$.

Definition 3.14 (Language of the Library of Babel)
The language of the Library of Babel Σ_{B} is $\Omega_{\mathrm{B}}^{1.312\times10^6}$.

Definition 3.14 states that the language of the Library of Babel contains exactly the books with a length of 1.312×10^6 positions. In light of this definition, it is clear that even though the language of the Library of Babel is "very-much-more-than-astronomically" (Dennett 1995: 109) vast, it is finite. To be exact, the language of the Library of Babel contains

$$|\Omega_{\mathrm{B}}|^{|b|} = 25^{1.312\times10^6} \tag{3.1}$$

books. Therefore, the language of the Library of Babel is not really the logical space of all books. Rather, it is the logical space of all books over the alphabet of the Library of Babel with a length of 1.312×10^6 positions. The logical space of all books is either the Kleene closure of the alphabet of the Library of Babel or the Kleene closure of the union of all alphabets. I will return this observation in section 3.3 when discussing the idea that the Library of Mendel is "the logical space of all genomes" (Dennett 1995: 123).

There are two additional facts about the language of the Library of Babel important to Dennett's interpretation which I will discuss in turn.

The first fact is that most books in the language of the Library of Babel are meaningless. That is, most (sub)books are sequences of symbols that do not constitute grammatically well-formed sentences (or even words found in a dictionary) and are hence trivially

meaningless. What is more, most grammatically well-formed books are also meaningless.

The second fact is that the books in the language of the Library of Babel are such that we can travel from one book to another book. That is, there is a binary relation on the language of the Library of Babel interpreted as travel relation. This idea can be found in the short story and in Dennett's interpretation: The narrator states that "[l]ike all the men of the Library [of Babel], in my younger days I traveled" (Borges 1998: 112) in search of a specific book; and Dennett asks us to "[i]magine traveling by spaceship through the Moby Dick galaxy of the Library of Babel" (1995: 110). The Library of Babel is hence a relational structure:

Definition 3.15 (Library of Babel)
The Library of Babel is a relational structure $\langle \Sigma_{\mathrm{B}}, R_{\mathrm{B}} \rangle$ where the domain is the language of the Library of Babel Σ_{B} and the binary relation is the travel relation R_{B}.

It is clear that an appropriate definition of the travel relation is a far from trivial task: What, exactly, does it mean to travel from one book to another? Is there a traveler or is this just a metaphor? What are the formal properties of the travel relation? And so on. An equally daunting challenge has to be met in defining the Library of Mendel as will be made explicit in section 3.3.4.

3.3 Dennett's definition of biological possibility

In this section, I will unpack Dennett's definition of biological possibility:

Definition 3.16 (Biological possibility)
Some "x is biologically possible if and only if x is an instantiation of an accessible genome or a feature of its phenotypic products" (Dennett 1995: 118).

At the core of his definition is the Library of Mendel which can be roughly characterized as "the logical space of all genomes" (Dennett 1995: 123). Dennett presents it in form of a rather baroque thought experiment. In subsection 3.3.1, I will strip the Library of Mendel down to its bare essentials by restating it as relational structure. I will then use this relational structure to make definition 3.16 more explicit in subsection 3.3.2 and explain its advantages in subsection 3.3.3. Finally, in subsection 3.3.4, a number problems

with the definition will be discussed, most importantly the missing interpretation of the accessibility relation.

3.3.1 The Library of Mendel

I will now restate the Library of Mendel as relational structure where the domain is its language and the binary relation the accessibility relation. In order to get at the language of the Library of Mendel, an alphabet and strings over this alphabet need to be defined:

Definition 3.17 (Alphabet of the Library of Mendel)
The alphabet of the Library of Mendel Ω_{M} is $\{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}$.

Definition 3.18 (Description of a genome)
A description of a genome g in the Library of Mendel is a string over Ω_{M}.

A genome is the totality of genetic information of a living being encoded in a chain of nucleotides called deoxyribonucleic acid or DNA. Nucleotides are in part composed of one of the four nucleobases adenine, cytosine, guanine and thymine; four types of nucleotides are distinguished on the basis of these nucleobases (Alberts et al. 2008: 173–177). Each type of nucleotide is represented by an unitalicized typewriter font capital letter `A`, `C`, `G` or `T` respectively. A genome can hence be described or represented as string over the alphabet of the Library of Mendel, namely as a sequence of representations of nucleotides. For example, the human genome (more precisely, the human chromosome 1 reference sequence) starts with the string `TAACCCTAAC` (Gregory et al. 2006). This idea is of course not originally Dennett's; parlance of a genetic alphabet is widespread in the biological sciences at least since the 1960s. In order to avoid confusion, I will clearly distinguish between the alphabet of the Library of Mendel and the scientific notion of a genetic alphabet in what follows. With definitions 3.17 and 3.18 at hand, the language of the Library of Mendel can be stated:[2]

[2] Dennett remarks that Library of Mendel is a wing of the Library of Babel. That is, since the alphabet of the Library of Mendel is a subset of the alphabet of the Library of Babel, every description of a genome is either a substring of a book or a concatenation of some (sub)books in the language of the Library of Babel. While this remark is certainly true, it makes for a very messy distribution of descriptions of genomes over several books. For example, the human genome has roughly 3×10^9 base pairs, so its description has a length of 3×10^9 positions. Since a book b in the Library of Babel has a length of 1.312×10^6 positions, it holds that $b_1 \oplus b_2 \oplus \cdots \oplus b_{2286} \oplus b_{2287}[1, 768000]$ is the simplest

Definition 3.19 (Language of the Library of Mendel)
The language of the Library of Mendel Σ_{M} is Ω_{M}^{*}.

Definition 3.19 states that the language of the Library of Mendel includes every string over the alphabet of the Library of Mendel. For example, it includes descriptions of all the "nucleotide sequences for over 300 000 formally described species" (Benson et al. 2015) available at GenBank which is the most comprehensive gene data base. This is not surprising; after all, the language of the Library of Mendel is countably infinite. However, is Dennett correct in calling the language of the Library of Mendel the logical space of all descriptions of genomes? This might seem like a frivolous question, but it is not. To see this, note the qualifier that the language of the Library of Mendel "ignores the (apparent) possibility of alternative genetic alphabets" (Dennett 1995: 112). What Dennett seems to allude to is the idea of life forms not based on carbon, but for example on silicon or boron (e.g., see Trevors and Abel 2004). The DNA-analogue of such aliens would be chemically different from terrestrial DNA and hence constitute a distinct genetic alphabet. Descriptions of their genomes are hence not captured by the language of the Library of Mendel. More down to earth, take the RNA-world hypothesis, namely the idea that "DNA- and protein-based life was preceded by a simpler life form based primarily on RNA" (Joyce 2002). Again, albeit only having a partially different genetic alphabet, genomes of RNA-world life forms are not included in the language of the Library of Mendel.

There are at least three additional limiting cases. The first one concerns the expansion of the genetic alphabet. As case in point, consider a recent result in synthetic biology: The genetic alphabet can be expanded in vitro to a six-letter alphabet by adding two nucleotides (d5SICS and dNaM to wit) forming a so-called unnatural base pair which is argued to be functionally equivalent to a natural base pair (Malyshev et al. 2012). For the second case, consider hypothetical organisms where phosphorus in the backbone of nucleic acids is replaced by arsenic, giving rise to a distinct biochemistry of life (Wolfe-Simon et al. 2009). In third and final case, the reading frame is changed. That is, instead of encoding information in triplets, it could be encoded in longer or shorter sequences. Note that this also involves the expansion or contraction of the genetic alphabet. For example, assuming that 20 amino acids are required, "[o]nly a triplet code using four bases and a doublet code using six bases have coding capacities in the right range"

description of the human genome in the Library of Babel. From a modeling perspective, it is hence well-justified to introduce a separate and simpler language of the Library of Mendel.

Cleland and Copley (2005: 166). In other words, other combinations of reading frames and genetic alphabets are either too simple or too complex.

These cases show that the language of the Library of Mendel occupies a significantly smaller space than the logical space of all descriptions of genomes.

With the domain of the relational structure that is the Library of Mendel in place, let us turn to its binary relation. Consider again Dennett's definition of biological possibility. He states that "x is biologically possible if and only if x is an instantiation of an accessible [description of a] genome or a feature of its phenotypic products" (Dennett 1995: 118). What it means, exactly, for a description of a genome to be accessible will be discussed in detail later in this section. For now, all that matters is that there is a binary relation, interpreted as accessibility relation, on the language of the Library of Mendel.[3] This completes restating the Library of Mendel as relational structure:

Definition 3.20 (Library of Mendel)
The Library of Mendel is a relational structure $\langle \Sigma_{\mathrm{M}}, R_{\mathrm{M}} \rangle$ where the domain is the language of the Library of Mendel Σ_{M} and the binary relation is the accessibility relation R_{M}.

3.3.2 Restating Dennett's definition

With the help of definition 3.20, Dennett's definition of biological possibility as per 3.16 can be made explicit (meant in a normative and not in an exegetical sense):

Definition 3.21 (Biological possibility)
Some x is biologically possible at $g \in \Sigma_{\mathrm{M}}$ if and only if there is some $g' \in \Sigma_{\mathrm{M}}$ such that $gR_{\mathrm{M}}g'$ and x is an instance of g' or a feature of the phenotypic products of g'.

Definition 3.21 provides a prototypical relational semantics for biological possibility. The qualifier 'prototypical' attaches to 'semantics' rather than 'relational': Definition 3.21 does not state truth conditions of sentences, but rather specifies necessary and sufficient conditions on non-linguistic entities. For now, I will gloss over this distinction; it will be discussed in more detail in chapter 5.

[3] There also is a phenotypic variant of Library of Mendel due to Dawkins (1996) which he calls 'museum of possible life forms'.

Let me clarify the structure and terminology of definition 3.21. Consider first the left hand side of the biconditional and note that biological possibility is defined with respect to g, namely a specific description of a genome in the language of the Library of Mendel.

On the right hand side of the biconditional, the condition for some x to be biologically possible at g is stated. It is instructive to distinguish three separate subconditions which I propose to call existential, relational and material subcondition respectively:

1. The existential subcondition requires that there is a description of a genome g' in the Library of Mendel which satisfies the relational subcondition and the material subcondition.

2. The relational subcondition requires that g' is accessible from g via the accessibility relation.

3. The material subcondition is a disjunction:

   (a) The first disjunct is satisfied if x is an instance of g'; an instance of g' is a genome represented by g'.

   (b) The second disjunct is satisfied if x is a feature of the phenotypic products of g'. This requires some explanation. The phenotype of an organism describes its "manifested morphology, physiology, and behavior" (Sterelny and Griffiths 1999: 388) such as eye-color or mating behavior. The phenotype is contrasted with the genotype of an organism, that is a description of its genome. The relation between genotype and phenotype is extremely complex; put very roughly, it is a many-to-many relation due to various developmental, environmental and stochastic causes (Lewontin 2011). Dennett's strategy is to simplify this relation by postulating a "reader-constructor" (1995: 113) which turns descriptions of genomes into phenotypic products. Therefore, the second disjunct is satisfied if x is a feature of the products of applying the reader-constructor to g'.

This completes restating Dennett's definition of biological possibility.

3.3.3 Advantages

Before turning to its problems, I should make explicit that definition 3.21 (respectively the relational structure it is based on) is an interesting proposal well worth the effort of

being fleshed out in light of the desiderata compiled in section 1.3. In what follows, I will highlight three advantages:

First, since biological possibility is defined with respect to a specific description of a genome in the language of the Library of Mendel, definition 3.21 offers a what is called 'local' or 'internal' perspective on biological possibility (see Blackburn et al. 2001). This has two important consequences:

1. What is biologically possible at one description of a genome need not be possible at another description of a genome. Biological possibility as stated in definition 3.21 is hence relative to (or sensitive to the context of) descriptions of genomes. To this effect, Dennett remarks that his notion of biological possibility has "an important property: some things will be 'more possible' than others — that is, nearer in the multidimensional search space, and more accessible, 'easier' to get to" (1995). I have already discussed the ins and outs of grading biological possibility in chapter 2. In chapter 6, I will show how grading of biological possibility in the spirit of definition 3.21 can be implemented more precisely.

2. More general notions of biological possibility can be built from the local perspective. For example, we could distinguish between a notion of biological possibility proper and a notion of biohistorical possibility (see section 2.2): x is biologically possible at some description of a genome versus x is biologically possible at a certain subset of descriptions of genomes. Or we could distinguish between a notion of terrestrial biological possibility and a notion of extraterrestrial biological possibility by replacing the Library in Mendel with a different relational structure; and so on. I will implement a number of notions of biological possibility on the basis of definition 3.21 in chapter 5.

Second, in relational semantics, possibility and necessity are interdefinable ($\Box\phi$ is defined as $\neg \Diamond \neg\phi$); so with definition 3.21, biological necessity comes for free:

Definition 3.22 (Biological necessity)
Some x is biologically necessary at $g \in \Sigma_{\mathrm{M}}$ if and only if for all $g' \in \Sigma_{\mathrm{M}}$ such that $gR_{\mathrm{M}}g'$, x is an instance of g' or a feature of the phenotypic products of g'.

Note that the interdefinability also holds for any more general notion of biological possibility built from the local perspective. Other biological modalities require more work, but are still attainable using the Library of Mendel. For example, in chapter 9, I will

define biological counterfactuality in the style of Lewis (1973, 1979) but avoid some of the traditional problems, most notably any ambiguity with respect to similarity.

Finally, the perhaps most exciting advantage is that definition 3.21 can be turned into a full blown modal logic of biological modalities. From this two things follow:

1. Such a modal logic will not only enable us to spell out the inferential relationship between sentences using a certain kind of biological modality; it will also allow us to map the inferential relationship between different notions of (say) biological possibility. For example, if something is biohistorically possible, it must also be biologically possible, but not vice versa.

2. A modal logic of biological modalities will also put us in a position to tackle the challenge of unraveling the inferential relationship between biological and non-biological modalities without falling prey to the problems outlined in chapter 2.

In short, the local perspective is an advantage because it facilitates the construction of a versatile tool kit suitable to dealing with (at least some and hopefully most of) the examples of biological possibility discussed in chapter 1. So even if there are (at least in scientific practice) many and incompatible notions of biological possibility, we will still have a unified framework to compare and assess them. Furthermore, biological necessity and other biological modalities can be captured by the same framework. Last but not least, this framework enables us to map the inferential relationships between the aforementioned modal notions.

3.3.4 Problems

I will now discuss some problems of definition 3.21 in descending order of importance. It is instructive to consider them in order to attain guidelines for how to improve upon definition 3.21. Note that these problems do not pertain to the adequacy of this definition; rather, only by solving these problems, we will get into a position to argue about the adequacy of definition 3.21.

However, before doing so, briefly consider two objections Dennett (1995: 121ff.) anticipates with respect to his definition that also apply to definition 3.21. The first objection is that definition 3.21 plays to gene centrism in the way it is based on the Library of Mendel. Now gene centrism is "the doctrine that genes play some special role in ontogeny, which is often described in terms of information-bearing or programming"

(Weber forthcoming). Dennett's reply is simply that gene centrism is (more or less) correct, and I tend to agree. The second objection is that definition 2.3 is not phrased in terms of biological laws. Dennett observes that definition 2.3 "does not rule out biological laws; it merely sets the burden of proof for those who want to propose any" (1995). Let me offer an even stronger reply based on section 2.1: Even if there are biological laws, defining biological possibility in terms of biological laws runs into the problem either of reducing biological possibility to physical (or logical possibility), or of being circular, for most accounts. As already stated, this does not exclude the possible explanatory role of biological laws with respect to other, non-modal explananda.

I now turn to new problems with definition 2.3:

1. How is the accessibility relation defined? The accessibility relation carries much weight in definition 3.21 in form of the relational subcondition. Therefore, without a definition of the accessibility relation, the relational subcondition cannot be satisfied and definition 3.21 does not get off the ground. Dennett recognizes that "[w]e have to specify a starting point in the Library of Mendel, and a means of 'travel'" (1995). Unfortunately, he does not provide the required definition but persists in using the travel-metaphor.

   In order to overcome this challenge, two steps need to be taken: First, a salient interpretation of the accessibility relation must be provided. In section 3.4, I will argue for an interpretation in terms of a solution to a string editing problem. In a second step, the required necessary and sufficient conditions can then be stated.

2. Is the reader-constructor an abstraction or an idealization? The second problem concerns the reader-constructor. Dennett concedes that the reader-constructor "is a brutal oversimplification" but adds that "later we can reopen the question of the developmental or embryological complications" (1995: 115). In a nutshell, his strategy is hence to provide a simplified definition of biological possibility; if it proves to be fruitful, work on removing the simplifications is to be undertaken.

   An important implicit assumption of this strategy is that these simplifications can indeed be removed. In order to make this assumption more precise, I will use the distinction between abstractions and idealizations due to Stokhof and van Lambalgen (2011).[4] They observe that models always neglect certain variables

[4] There are many rivaling ways to carve out the difference between abstractions and idealizations (e.g., see Godfrey-Smith 2009). I am using the distinction at hand merely as a tool without any further commitments.

of the modeled phenomenon. This can be achieved in one of two ways. Either the variable is included in the model and assigned a value which is false, or the variable is not included in the model at all. The first way is an abstraction, the second is an idealization. Therefore, while it is "possible, at least in principle if not always in practice, to 'undo' an abstraction" (Stokhof and van Lambalgen 2011: 9) without building a new model, the inclusion of an idealization always requires a new model. For example, "random mating, non-overlapping generations, infinite population size, perfect Mendelian segregation, frequency-independent genotype fitnesses, and the absence of stochastic effects" (Okasha 2012) are abstractions in simple population genetic models. These abstractions can be undone, for example by assigning a less-than-infinite value to the variable of population size.

With respect to the reader-constructor, Dennett's implicit assumption is that the mentioned simplifications are abstractions rather than idealizations. If these simplifications were idealizations, their inclusion would require a new definition of biological possibility. It is hence paramount to provide at least some indication of how Dennett's simplification could be removed. I will do so in chapter 7.

3. What about the environment? To complicate matters further, the environment encompasses other organisms which in turn change the environment. Dennett suggests to start with actual environments "in order to extrapolate cautiously to earlier and later possibilities" (1995: 116). Both the mechanism for creating environments and the method for cautiously extrapolating environments are black-boxed. Here Dennett overlooks something quite important, namely that there is an entanglement between biological possibility and what could be called geological, geographical, or ecological possibility depending on how the notion of an environment is defined exactly (let us settle for ecological possibility). In section 2.2, we have seen that we can distinguish historical from ahistorical biological possibility where the latter is relative to a particular evolutionary history. In a similar vein, ecological possibility is relative to a particular environment. How ecology fits into the hierarchy of grades of biological possibilities is far from clear, however. More generally, constraints on biological possibility such as evolutionary history or environment translate into distinct notions of biological possibility in addition to the ones introduced above.

4. Populations or individuals? As discussed in section 2.2, there a different notions of biological possibility depending on the scale of the biological phenomena under

consideration. It could be objected that definition 3.21 is unable to handle phenomena on a scale larger than an individual organism since possibility is defined on the basis of an individual genome. This objection is countered by simply plugging (one of) the reference genome(s) of a species or population into definition 3.21. This is not to deny that there are substantial epistemic and technological challenges involved in assembling any reference genome (for an overview, see Church et al. 2011 and Baker 2012). However, these potential difficulties do not stem from definition 3.21 but rather from the implicit assumption that there are biological phenomena at the scale of species or populations.

In short, the missing interpretation of the accessibility relation is the most pressing problem and will be addressed in the next section. Other problems, if not already answered, will be tackled in chapter 7.

3.4 Interpreting the accessibility relation

This section addresses the most pressing problem with respect to definition 3.21, namely the missing interpretation of the accessibility relation: I will propose to interpret the accessibility relation as solution to a string editing problem. In subsection 3.4.1, the string editing problem is introduced; in subsection 3.4.2, some arguments in favor of my proposal are provided.

3.4.1 String editing problem

Roughly put, a string editing problem is finding the lowest cost transformation of an initial string i into a target string t (Szpankowski 2010). The most basic transformation of a string is an edit operation:

Definition 3.23 (Edit operation)
Let i, t, x, y be strings and let s, s' be strings such that $|s| \leq 1$ and $|s'| \leq 1$ but not $|s| = |s'| = 0$. An edit operation $\mathcal{E}$ is a pair $\langle s, s' \rangle$. An edit operation from i to t, denoted by $i \xrightarrow{\mathcal{E}} t$, is $\mathcal{E}$ such that $i = x \oplus s \oplus y$ and $t = x \oplus s' \oplus y$ (Wagner and Fischer 1974: 169).

The standard edit operations are substitution ($s \neq \lambda$ and $s' \neq \lambda$), deletion ($s \neq \lambda$ and $s' = \lambda$) and insertion ($s = \lambda$ and $s' \neq \lambda$). Multiple edit operations can be composed into

an edit script:

Definition 3.24 (Edit script)
Let i, t, x be strings. An edit script $\mathcal{S}$ is a sequence of edit operations $\langle \mathcal{E}_1, \mathcal{E}_2, \ldots, \mathcal{E}_n \rangle$ where $n \in \mathbb{N}_1$. An edit script from i to t, denoted by $i \xrightarrow{\mathcal{S}} t$, is $\mathcal{S}$ such that $x_{i-1} \xrightarrow{\mathcal{E}_i} x_i$ for $0 < i < n$ where $x_0 = i$ and $x_n = t$ (Wagner and Fischer 1974: 169).

For illustration of definitions 3.23–3.24, consider the strings ⌈Geneva⌉, and ⌈Genoa⌉ the following two edit scripts:

$$\mathcal{S}_1 = \langle \langle \lceil \mathrm{e} \rceil, \lambda \rangle, \langle \lceil \mathrm{v} \rceil, \lambda \rangle, \langle \lambda, \lceil \mathrm{o} \rceil \rangle \rangle \tag{3.2}$$

$$\mathcal{S}_2 = \langle \langle \lceil \mathrm{e} \rceil, \lceil \mathrm{o} \rceil \rangle, \langle \lceil \mathrm{v} \rceil, \lambda \rangle \rangle \tag{3.3}$$

$\mathcal{S}_1$ reads 'delete ⌈e⌉; delete ⌈v⌉; insert ⌈o⌉' and is an edit script from ⌈Geneva⌉ to ⌈Genoa⌉ since:

$$\lceil \mathrm{Geneva} \rceil \xrightarrow{\langle \lceil \mathrm{e} \rceil, \lambda \rangle} \lceil \mathrm{Genva} \rceil \xrightarrow{\langle \lceil \mathrm{v} \rceil, \lambda \rangle} \lceil \mathrm{Gena} \rceil \xrightarrow{\langle \lambda, \lceil \mathrm{o} \rceil \rangle} \lceil \mathrm{Genoa} \rceil \tag{3.4}$$

whereas $\mathcal{S}_2$ reads 'substitute ⌈e⌉ with ⌈o⌉; delete ⌈v⌉' and is also an edit script from ⌈Geneva⌉ to ⌈Genoa⌉ since:

$$\lceil \mathrm{Geneva} \rceil \xrightarrow{\langle \lceil \mathrm{e} \rceil, \lceil \mathrm{o} \rceil \rangle} \lceil \mathrm{Genova} \rceil \xrightarrow{\langle \lceil \mathrm{v} \rceil, \lambda \rangle} \lceil \mathrm{Genoa} \rceil \tag{3.5}$$

Note that an edit script as per definition 3.24 is ambiguous if no target string is provided. For example, without specifying ⌈Genoa⌉ as target string, ⌈Gonea⌉ is also the result of applying $\mathcal{S}_2$ to ⌈Geneva⌉ since:

$$\lceil \mathrm{Geneva} \rceil \xrightarrow{\langle \lceil \mathrm{e} \rceil, \lceil \mathrm{o} \rceil \rangle} \lceil \mathrm{Goneva} \rceil \xrightarrow{\langle \lceil \mathrm{v} \rceil, \lambda \rangle} \lceil \mathrm{Gonea} \rceil \tag{3.6}$$

This can be avoided by providing an algorithmic definition of edit scripts; see appendix B. for an example (for the related discussion of opaque versus transparent modalities, see section 7.2.2). However, what follows holds both for definition 3.24 and for any algorithmic definition of edit scripts.

Now, $\mathcal{S}_1$ involves more edit operations than $\mathcal{S}_2$ to attain the same goal. So with respect to simplicity, $\mathcal{S}_1$ is better than $\mathcal{S}_2$. A principled way to compare edit scripts is by means of a cost function:

Definition 3.25 (Edit script cost)
Let E be the set of edit operations and let $\gamma : E \to \mathbb{R}_+$ be the cost function. The cost of an edit script $\mathcal{S} = \langle \mathcal{E}_1, \mathcal{E}_2, \ldots, \mathcal{E}_n \rangle$, denoted by $\gamma(\mathcal{S})$, is given by (Wagner and Fischer 1974: 169):

$$\gamma(\mathcal{S}) = \sum_{i=1}^{n} \gamma(\mathcal{E}_i) \tag{3.7}$$

According to definition 3.25, we stipulate a cost for each (type of) edit operation; the cost of an edit script is then the sum of the costs of its constituent edit operations. We can now define the minimum cost of an edit script:

Definition 3.26 (Edit distance)
Let i, t be strings. The edit distance from i to t, denoted by $\delta(i, t)$, is $\min\{\gamma(\mathcal{S}) : i \xrightarrow{\mathcal{S}} t\}$ if $|\{\gamma(\mathcal{S}) : i \xrightarrow{\mathcal{S}} t\}| > 0$, and undefined otherwise (Wagner and Fischer 1974: 169).

Definition 3.26 states that the edit distance from i to t is the cost of the least costly edit script(s) from i to t. It is important to underscore that edit distance is relative, first, to the set of viable edit operations from which edit scripts can be constructed, and, second, to the cost function; this will now be illustrated briefly:

First, consider the dependency of edit distance on the set of viable edit operations. Compare two important variants of edit distance, namely Hamming distance (after Richard Hamming 1950) and Levenshtein distance (after Vladimir Levenshtein 1966): Intuitively, Hamming distance is the number of positions at which two strings of equal length do not have the same symbol. Here the set of edit operations is restricted to substitution and the cost function is constant, namely $\gamma(\mathcal{E}) = 1$ for any $\mathcal{E}$. The Hamming distance between ⌈cat⌉ and ⌈car⌉ is 1, the Hamming distance between ⌈Geneva⌉ and ⌈Genoa⌉ is undefined. By contrast, Levenshtein distance is the number of changes required to transform i into t. The set of edit operations consists of substitution, deletion and insertion; the cost function is also constant. The Levenshtein distance between ⌈cat⌉ and ⌈car⌉ is 1, the Levenshtein distance between ⌈Geneva⌉ and ⌈Genoa⌉ is 2.

Second, consider the dependency of edit distance on the cost function. Let D be a set of strings which we interpret as words in a dictionary, say the Oxford English Dictionary. We want to compare different edit scripts from ⌈cat⌉ to ⌈heart⌉. The edit operations in play are substitution, insertion and deletion. However, we have a general preference for

edit scripts which have words in the dictionary as their intermediates. That is, we prefer edit scripts such as

$$\lceil \text{cat} \rceil \xrightarrow{\mathcal{S}_3} \lceil \text{heart} \rceil = \lceil \text{cat} \rceil \xrightarrow{\langle \lceil \text{c} \rceil, \lceil \text{h} \rceil \rangle} \lceil \text{hat} \rceil \xrightarrow{\langle \lambda, \lceil \text{e} \rceil \rangle} \lceil \text{heat} \rceil \xrightarrow{\langle \lambda, \lceil \text{r} \rceil \rangle} \lceil \text{heart} \rceil \tag{3.8}$$

over edit scripts such as

$$\lceil \text{cat} \rceil \xrightarrow{\mathcal{S}_4} \lceil \text{heart} \rceil = \lceil \text{cat} \rceil \xrightarrow{\langle \lambda, \lceil \text{e} \rceil \rangle} \lceil \text{ceat} \rceil \xrightarrow{\langle \lambda, \lceil \text{r} \rceil \rangle} \lceil \text{ceart} \rceil \xrightarrow{\langle \lceil \text{c} \rceil, \lceil \text{h} \rceil \rangle} \lceil \text{heart} \rceil \tag{3.9}$$

since $\lceil \text{hat} \rceil$ and $\lceil \text{heat} \rceil$ are words ins the dictionary whereas $\lceil \text{ceat} \rceil$ and $\lceil \text{ceart} \rceil$ are not. Our preference could be implemented by stipulating the following cost function:

$$\gamma(\mathcal{E}) = \begin{cases} 1 & \text{if } i \xrightarrow{\mathcal{E}} t \text{ and } t \in D \\ 100 & \text{otherwise} \end{cases} \tag{3.10}$$

We can now give a formal definition of the string editing problem:

Definition 3.27 (String editing problem)
Let i, t be strings. The string editing problem with respect to i, t is finding $i \xrightarrow{\mathcal{S}} t$ such that $\gamma(\mathcal{S}) = \delta(i, t)$.

Definition 3.27 states that the string editing problem with respect to i, t consists in finding the least costly edit script from i to t. Let us call any such edit script a solution (there need not be a unique least costly edit script). It should be noted that a string editing problem is usually solved computationally (e.g., Apostolico 2010); however, in what follows, we can assume that the solution to any string editing problem is given.

3.4.2 Accessibility relation as solution to a string editing problem

I propose to interpret the accessibility relation as a solution to a string editing problem along the following lines:

Definition 3.28 (Accessibility relation)
For $g, g' \in \Sigma_{\text{M}}$, $gR_{\text{M}}g'$ if and only if there is a solution to a string editing problem with respect to g, g'.

For clarification, let me preempt an objection. It could be argued that definition 3.28 is empty: For any pair of descriptions of genomes g, g' in the Library of Mendel, there is a least costly edit script from g to g'. Put differently, every string editing problem with respect to g, g' has a solution. Therefore, so the argument goes, the accessibility relation R_{M} is the trivial relation $\Sigma_{\mathrm{M}} \times \Sigma_{\mathrm{M}}$. The upshot of this objection is that R_{M} does not do any work with respect to defining biological possibility. Consider plugging definition 3.28 into definition 3.21: Some x is biologically possible at $g \in \Sigma_{\mathrm{M}}$ if and only if there is some $g' \in \Sigma_{\mathrm{M}}$ such that there is a least costly edit script from g to g' and x is an instance of g' or a feature of the phenotypic products of g'. If $R_{\mathrm{M}} = \Sigma_{\mathrm{M}} \times \Sigma_{\mathrm{M}}$, this is equivalent to: Some x is biologically possible at $g \in \Sigma_{\mathrm{M}}$ if and only if there is some $g' \in \Sigma_{\mathrm{M}}$ and x is an instance of g' or a feature of the phenotypic products of g'.

I have two replies this objection. First, the objection ignores the parameters, namely the set of available edit operations and the cost function. For example, if the required solution is framed in terms of Hamming distance or Levenshtein distance as explicated above, R_{M} is not the trivial relation. Since definition 3.28 does not specify these parameters, it should be understood as schema for how different notions of biological possibility can be cashed out depending on how we choose the values of the aforementioned parameters. So definition 3.28 can be read as follows: For $g, g' \in \Sigma_{\mathrm{M}}$, $gR_{\mathrm{M}}g'$ if and only if there is an edit script from g to g' that fits certain cost requirements and given a set of edit operations. However, and this is my second reply, I submit that there is indeed a notion of biological possibility that is captured by a trivial accessibility relation, namely the weakest notion of biological possibility in the proposed framework. All other notions of biological possibility are built from restricting definition 3.28 by specifying the parameters in question.

I will now turn to provide a two reasons for why my proposal is promising in light of the methodological desiderata spelled out in chapter 1:

First, the string editing problem is rooted in biological practice. For example, the standard algorithm for global alignment (a subproblem of the string editing problem), was developed by Needleman and Wunsch (1970) in order to align nucleotide sequences. Many other subproblems, such as inexact string matching or finding the longest common substring, play an important role in computational biology (see Gusfield 1997 for an overview).

To bring this point home, let me show that the accessibility relation can be understood as variant of genetic distance. Genetic distance (or evolutionary distance) is the measure

of difference between pairs of homologous DNA sequences (call them h and h'); it is used in various contexts, most notably phylogenetic analysis. Genetic distance comes in many different flavors (see Nei 1972 for the most widely used notion), but is usually cashed out in terms of the number or fraction of positions at which the nucleotides of h and h' differ. It is important to distinguish between observed genetic distance and true genetic distance (Strimmer and Haesler 2009: 112f.): Observed genetic distance is simply the Hamming distance between h and h'. By contrast, true genetic distance is (the cost of) the edit script from h to h. Biologists are mostly interested in true genetic difference since observed genetic distance neglects the evolutionary history of DNA sequences. To see this, consider an example. Let $h = \lceil \mathtt{AAA} \rceil$ and $h = \lceil \mathtt{TAA} \rceil$. Here the observed genetic distance between h and h' is 1; however, assume that the true genetic distance is 3, for example as follows:

$$\lceil \mathtt{AAA} \rceil \xrightarrow{\langle \lceil \mathtt{A} \rceil, \lceil \mathtt{G} \rceil \rangle} \lceil \mathtt{GAA} \rceil \xrightarrow{\langle \lceil \mathtt{G} \rceil, \lceil \mathtt{A} \rceil \rangle} \lceil \mathtt{AAA} \rceil \xrightarrow{\langle \lceil \mathtt{A} \rceil, \lceil \mathtt{T} \rceil \rangle} \lceil \mathtt{TAA} \rceil \tag{3.11}$$

In order to get at the true genetic distance between h and h', three steps have to be undertaken:

1. Establish the observed genetic distance between h and h'.
2. Choose a nucleotide substitution model. Such a model specifies the rate at which nucleotides change on a position of a sequence. For example, the most simple model is due to Jukes and Cantor (1969) and "specifies that the equilibrium frequencies of the four nucleotides are 25% each, and that during evolution any nucleotide has the same probability to be replaced by any other" (Strimmer and Haesler 2009: 117).
3. Infer or simulate the true genetic distance based on the observed genetic distance and the chosen substitution model.

How, then, does the accessibility relation compare to the notion of genetic distance? On the one hand, the accessibility relation is similar to observed genetic distance in that evolutionary history is neglected. That is, if g, g' are related, then they are related via the least costly edit script from g to g' and not via an evolutionary more likely but also more costly edit script. On the other hand, the accessibility relation is similar to true genetic distance in that an edit script (and not only its cost) is provided. There are also some significant dissimilarities, the most important of which are following: Observed genetic distance is an empirical notion whereas the accessibility relation is not. And true genetic distance is a probabilistic notion whereas the accessibility relation is not (in

section 6.3, however, I will show that the definition of the accessibility relation can be modified to take into account the transition matrix of nucleotide substitution models, giving rise to a probabilistic relational semantics of biological modalities).

Second, the proposed interpretation provides a well-defined modeling framework in the sense of section 1.3. By this I mean that the formal properties of the Library of Mendel and the accessibility relation are unambiguous. This is important with respect to the task of constructing modal logics of biological modalities. The interpretation in terms of a solution to a string editing problem is also versatile: Definition 3.28 can easily be modified by imposing constraints on the solution to the string editing problem. This is advantageous, because it can be shown that some of Dennett's simplifications are indeed only abstractions and not idealizations. In addition, some of the notions of biological possibility briefly discussed in sections 2.2 and 3.3.3 will be implemented exactly by imposing such constraints.

3.5 Summary

I improve upon Daniel Dennett's definition of biological possibility by proposing two modifications. First, I provide a clarification of his definition by reconstructing the Library of Mendel as relational structure. Second, I argue that the most important shortcoming of Dennett's definition, namely the underdefined accessibility relation, can be overcome by interpreting the accessibility relation as a solution to a string editing problem. According to the restated definition, x is biologically possible with respect to a genome g if and only if there is some genome g' such that there is an edit script from g to g' that fits certain cost requirements given a set of edit operations, and x is an instance of g or a feature of the phenotypic products of g'. This new definition is promising because it is rooted in biological practice and can be extended into a family of modal logics.

II. Logical models of hemoglobin variants

4. Preliminaries

In chapters 4–7, I will put into action Dennett's restated definition of biological possibility and my schema for interpreting the corresponding accessibility relation by providing a detailed case study. In the chapter at hand, I will set the stage for constructing a range of logical models of hemoglobin variants in chapters 5–7. In section 4.1, the modeling goals and restrictions are made explicit. In section 4.2, related work and some of the employed technical tools are briefly reviewed.

The rough outline for chapters 5–7 is as follows: In chapter 5, I will construct a simple logical model of hemoglobin variants which will serve as basis for the subsequent discussion. In chapter 6, a number of implementations of how to add grades to the simple model are investigated. Finally, in chapter 7, I will outline how the modeling restrictions imposed in chapter 4 can be lifted in order to provide logical models of any variant caused by any point mutation at the coding region of any gene. Furthermore, the limitations of the proposed approach are discussed.

4.1 Modeling goals and restrictions

Hemoglobin is the protein in red blood cells responsible for binding oxygen and hence functionally associated with respiration. In humans, normal adult hemoglobin (HbA) consists of two alpha globin chains and two beta globin chains as depicted in Figure 4.1; these are determined by the hemoglobin alpha gene (*HBA*) and the hemoglobin beta gene (*HBB*) (see Berg et al. 2012: 195–213 for more details). Mutations or deletions of either type of chain cause a variety of diseases including sickle-cell disease and thalassemia (see Rees et al. 2010).

In line with the desiderata expressed in section 1.3, the logical models of hemoglobin variants are aimed at answering the following questions:

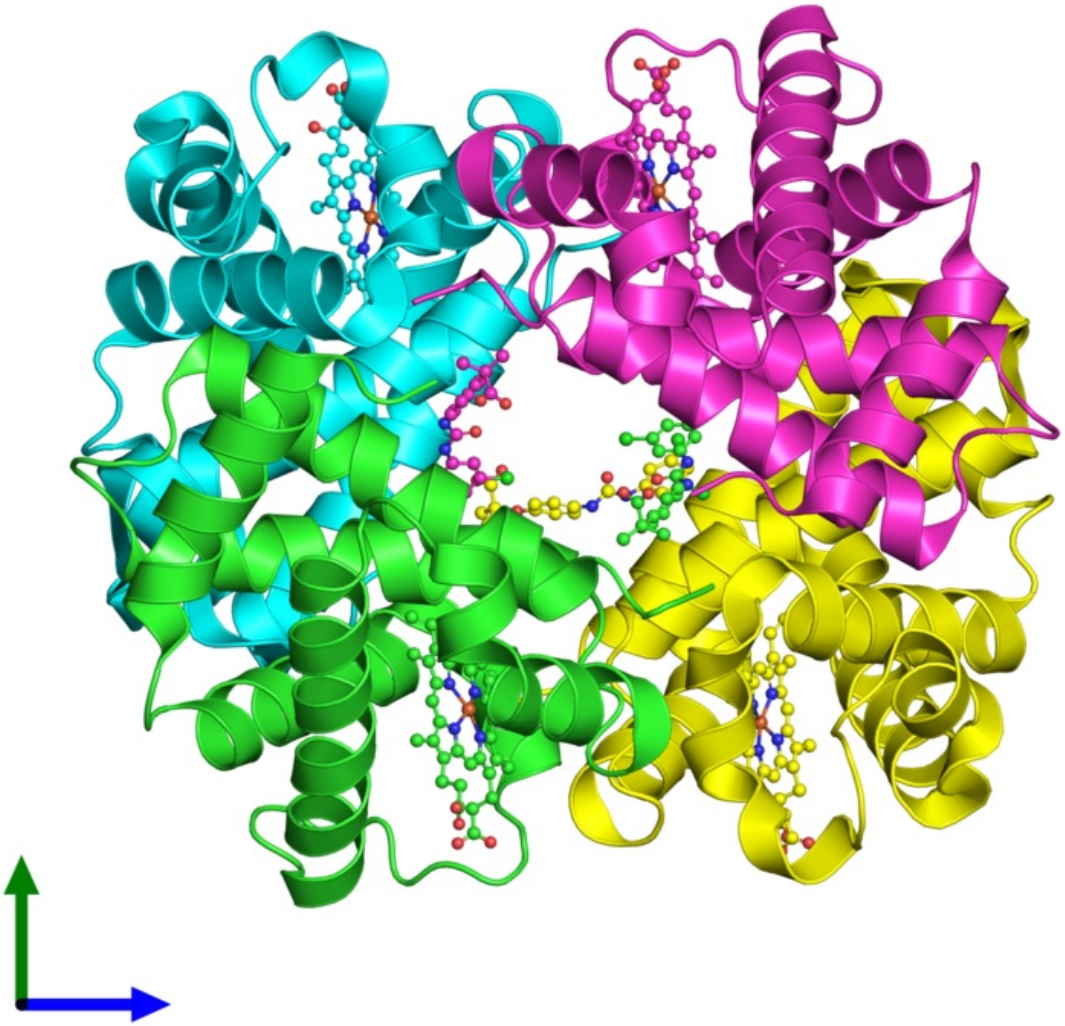


Figure 4.1

Structure of HbA with magenta and green alpha globin chains and turquoise and yellow beta globin chains (PDB 2d5z viewed from the front as per Gutmanas et al. 2014 based on Yokoyama et al. 2006).

- Which variants of hemoglobin are logically, physically and biologically possible?
- Are there multiple senses in which variants of hemoglobin are biologically possible? If yes, how can they be distinguished?
- How are the possible yet non-actual variants of hemoglobin to be explained?
- To what extent can the obtained results be generalized?

I now turn to discuss the modeling restrictions. It is crucial to note that the intended models are rather complex: There are 1226 HbA variants according to HbVar (database of human hemoglobin variants and thalassemia mutations as per April 2016, see Giardine et al. 2014). In order to reduce complexity, three restrictions will be employed (in chapter 7, it will be explained how they can be lifted):

First, the models are restricted to variants of HbA caused by single point mutations. A point mutation is the change of a single nucleotide of a nucleotide sequence. There are several ways to classify (point) mutations (e.g., Dunnen and Antonarakis 2000, 2001, Griffiths et al. 2010). Figure 4.2 provides a flowchart for the classification of point mutations that will be used in the remainder of this book. This classification is partial in the sense that it neglects both chromosomal mutations (e.g., translocations, transpositions) and gene mutations that change more than one nucleotide (e.g., duplications, sequence repeats, large indels). In addition, it is a hybrid between classifications at two distinct levels: The DNA level (changes of the nucleotide sequence of a gene) and the protein level (functional consequences of these changes).

In the following, the different classes of point mutations are briefly explained. Take a mutated nucleotide sequence m of a wild type w. At the DNA level, point mutations are either substitutions or indels (insertions or deletions):

- Substitution: m is the result of substituting a single nucleotide of w. Example: m = `CAA`, w = `AAA`. Note that an empty substitution (here any substitution of `A` with `A` in w) is not classified as substitution since it does not constitute a change of the wild type.[1]
- Indel: m is the result of inserting respectively deleting a single nucleotide of w. Example: m = `CAAA` respectively m = `AA`, w = `AAA`.

In addition, substitutions are either transversions or transitions depending on whether

[1] This might be debatable since an empty substitution does constitute a token change of the wild type even if it does not constitute a type change of the wild type.

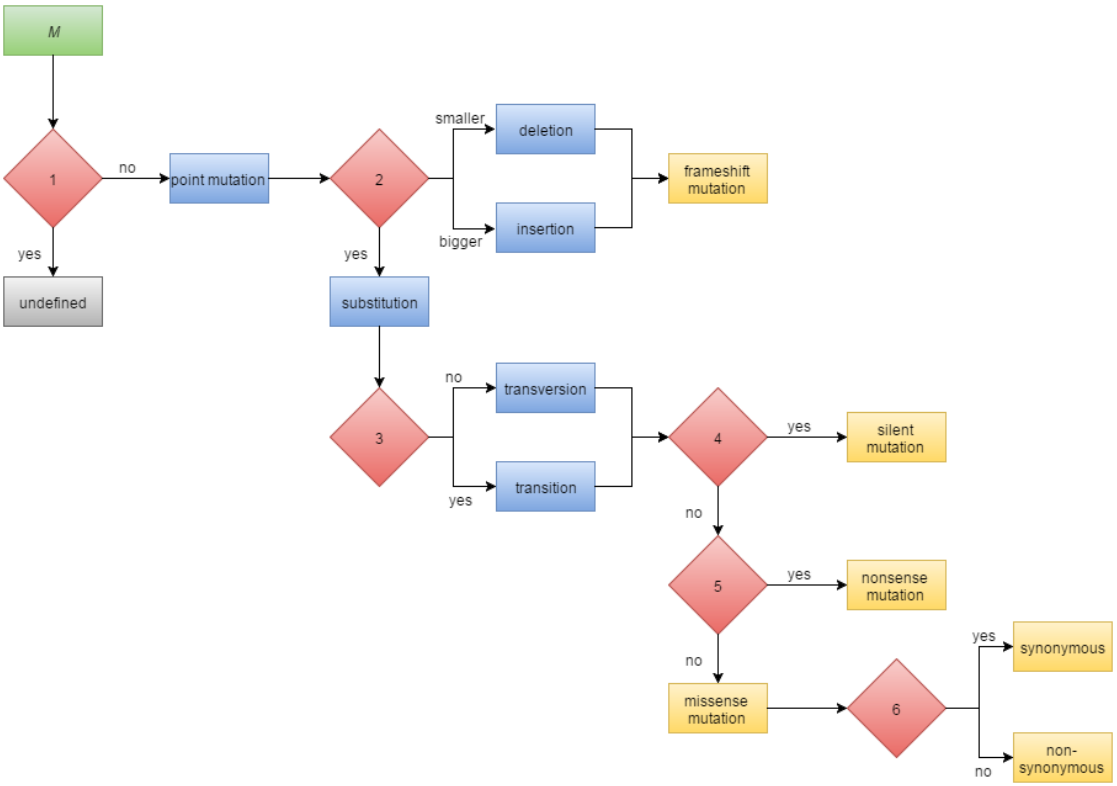


Figure 4.2

Flowchart for a classification of point mutations based on Dunnen and Antonarakis (2000, 2001) and Griffiths et al. (2010). The input (green) is a mutated nucleobase sequence m of a wild type w. Outputs are (sub-)classifications of the mutation on the DNA level (blue) and the protein level (yellow). Decision nodes (red) are labeled 1–6 and interpreted as follows:

1. Are m and w different at more than one base position?
2. Do m and w have the same length?
3. Is the substitution in m of the same chemical type (purine respectively pyrimidine) as the substituted base in w?
4. Do m and w specify the same (chain of) amino acid(s)?
5. Does m cause a chain termination as compared to w?
6. Is the (chain of) amino acid(s) specified by m functionally similar to the one specified by w?

For example, m = `AAA` given w = `AGA` is classified as point mutation/substitution/transition/missense mutation/synonymous mutation.

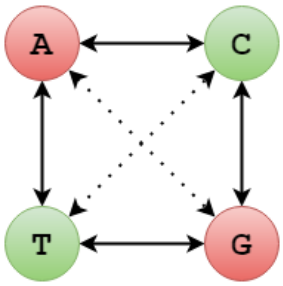


Figure 4.3
Possible transitions (dotted line) and transversions (solid line) based on Lemey et al. (2009). A transition is a substitution either from purine to purine or from pyrimidine to pyrimidine; a transversion is a substitution either from purine to pyrimidine or from pyrimidine to purine. Adenine (`A`) and guanine (`G`) are purines (red), cytosine (`C`) and thymine (`T`) are pyrimindines (green). Both transitions and transversions are symmetric and irreflexive.

or not the substitution in m matches the chemical type (purine respectively pyrimidine) of the substituted base in w. Figure 4.3 provides more details.

At the protein level, indels are frameshift mutations. By contrast, substitutions are in-frame mutations since substituting a nucleotide does not change the length of the nucleotide sequence. Substitutions are either silent mutations, nonsense mutations or missense mutations:

- Silent mutation: m and w code for the same (chain of) amino acid(s). Example: Both m = `AAG` and w = `AAA` code for lysine.
- Nonsense mutation: m terminates translation whereas w does not. Example: m = `TAA` terminates translation, w = `AAA` codes for lysine.
- Missense mutation: m and w each code for a different (chain of) amino acid(s). Example: m = `CAA` codes for glutamine, w = `AAA` codes for lysine.

Missense mutations are either synonymous mutations or nonsynonymous mutations depending on whether or not the translation of m is functionally equivalent to the translation of w; note that this is depending on the context.

Second, the models are restricted to variants of HbA caused by mutations of the nucleotides 19–21 (codon 6) of the coding region of *HBB*.[2] The restriction to a single codon

[2] The initiation codon is not counted.

of a gene is required since models of either *HBA* or *HBB* would still be rather complex: For example, *HBB* has a length of 1606 nucleotides, beta globin has a length of 146 amino acids (excluding the initiator methionine), and there are 860 known variants of HbA caused by mutations of *HBB*. The nucleotide sequence of codon 6 is `GAG` and codes for glutamine. Note that the choice of *HBB* over *HBA* and the choice of codon 6 over any of the other 145 codons is arbitrary, at least from a modeling perspective. However, codon 6 is interesting for biological and historical reasons: HbS, a variant of HbA caused by a substitution of adenine with thymine at nucleotide 20 of the coding region of *HBB* (and hence on codon 6) is the most common form of sickle-cell disease (Rees et al. 2010: 2020); and peptide fingerprinting of HbS led Vernon Ingram (1956, 1957) to the discovery that protein function can be drastically altered by the change of a single amino acid (Morange 1998: 125).

Putting together both restrictions, the task is to provide logical models of HbA variants caused by single point mutations at codon 6 of *HBB*. Note that 'caused' is to be understood as 'fully caused' in the following sense: An HbA variant that is caused by a single point mutation at codon 6 in conjunction with some other mutation does not fit the bill of 'fully caused'. For example, HbArlingtonPark is caused by a single substitution at codon 6 in conjunction with a single substitution at codon 95 of *HBB*. According to HbVar, there are at least seventeen HbA variants partially caused by a single substitution at codon 6. Table 4.1 provides a list of all known HbA variants that fit the restrictions. Note that all these variants except one are due to substitutions. For simplicity, and as third restriction, let us exclude frameshift mutations. The final form of the task is hence to provide logical models of HbA variants caused by single substitutions at codon 6 of *HBB*.

4.2 Related work

In this section, I will provide a brief overview over logical models in molecular biology. This serves as foil for my logical models presented in the next chapters. We can distinguish two (families of) logical models in molecular biology, namely models in the framework of ambient calculus and Zsyntax.

Ambient calculus is a process algebra and was created by Luca Cardelli and Andrew

[3] Beta 6 (-A); modified C-terminal sequence: (6)Gly-Arg-Ser-Leu-Pro-Leu-Leu-Pro-Cys-Gly-Ala-(17)Arg-COOH.

HbA variant	DNA level	Protein level	Class of point mutation
Codon 6 (-A)	HBB:c.20del`A`	beta 6 (-A)[3]	deletion/frameshift mutation
HbMachida	HBB:c.19`G` ⇝ `C`	beta 6 Glu>Gln	subst./transversion/mis./syn.
HbC	HBB:c.19`G` ⇝ `A`	beta 6 Glu>Lys	subst./transition/mis./nonsyn.
HbG-Makassar	HBB:c.20`A` ⇝ `C`	beta 6 Glu>Ala	subst./transversion/mis./syn.
HbS	HBB:c.20`A` ⇝ `T`	beta 6 Glu>Val	subst./transv./mis./nonsyn.
HbLavagna	HBB:c.20`A` ⇝ `G`	beta 6 Glu>Gly	subst./transition/missense/syn.

Table 4.1

Known variants of HbA caused by single point mutations at codon 6 of *HBB* based on HbVar (see Giardine et al. 2014). Column one specifies the name of the HbA variant. The second column indicates the mutation at the DNA level. Column three indicates the mutation at the protein level. The fourth column classifies the mutation according to Figure 4.2; the classification as synonymous respectively nonsynonymous depends on whether or not the clinical presentation of the variant is normal. Nomenclature follows the HGNC guidelines (see Povey et al. 2001); see Table 4.2 for amino acid abbreviations.

Gordon in order to model "mobile agents, the ambients where agents interact and the mobility of the ambients themselves" (2000: 177). For example, ambient calculus can be used to model mobile computation over the Internet. Ambient calculus was then applied to molecular biology by Aviv Regev et al. and this so called bioambient calculus "is suitable for representing various aspects of molecular localization and compartmentalization, including the movement of molecules between compartments, the dynamic rearrangement of cellular compartments, and the interaction between molecules in a compartmentalized setting" (2004: 143). That is, bioambient calculus can be used to model biochemical mechanisms, the bioambients such as cells, organelles or vesicles where the biochemical transitions take place, and the mobility of the bioambients themselves. Bioambient calculus has also been extended by modal logics. For example, Radu Mardare et al. (2005) propose a model checker for biological systems by extending bioambient calculus with temporal modal logic; as a further example, Anya Yermakova and Alexandru Baltag (2012) combine bioambient calculus with dynamic epistemic logic in order to model information flow in biological systems.

Let me now turn to Zsyntax. Zsyntax was created by Giovanni Boniolo et al. (2010, 2013, 2015) and is a formal language aimed to model biochemical reactions as deductions. For

Abbreviation	Symbol	Name	Codon(s)
Ala	A	alanine	GCA, GCC, GCG, GCT
Arg	R	arginine	AGA, AGG, CGA, CGC, CGG, CGT
Asn	N	asparagine	AAC, AAT
Asp	D	aspartate	GAC, GAT
Cys	C	cysteine	TGC, TGT
Gln	Q	glutamine	CAA, CAG
Glu	E	glutamate	GAA, GAG
Gly	G	glycine	GGA, GGC, GGG, GGT
His	H	histidine	CAC, CAT
Ile	I	isoleucine	ATA, ATC, ATT
Leu	L	leucine	CTA, CTC, CTG, CTT, TTA, TTG
Lys	K	lysine	AAA, AAG
Met	M	methionine	ATG
Phe	F	phenylalanine	TTC, TTT
Pro	P	proline	CCA, CCC, CCG, CCT
Ser	S	serine	AGC, AGT, TCA, TCC, TCG, TCT
Thr	T	threonine	ACA, ACC, ACG, ACT
Trp	W	tryptophan	TGG
Tyr	Y	tyrosine	TAC, TAT
Val	V	valine	GTA, GTC, GTG, GTT
Ter	*	termination	TAA, TAG, TGA

Table 4.2
Symbolic amino acid abbreviations, symbols, names, and possible codons (IUPAC 1984).

example, Zsyntax can express chemical equations such as (Boniolo et al. 2015: 402):

$$2H_2O + O_2 \rightarrow H_2O \tag{4.1}$$

The most interesting feature of Zsyntax is that it allows for context-sensitive reactions which are modeled by via a non-monotonic conjunction operator. Boniolo et al. rely on a decidedly syntactic or proof theoretic perspective. By contrast, my discussion of biological modalities so far as been and will be mostly semantic driven (perhaps with the exception of chapter 8).

To preempt an objection, there is of course a plethora of mathematical models in molecular biology such as nucleotide substitution models (e.g., Strimmer and Haesler 2009). However, these models are described in terms of a mixture of natural language and

mathematics; in short, they lack a formal language and do hence not qualify as logical models.

4.3 Summary

I propose to put into action the results obtained so far by constructing logical models of hemoglobin variants. Hemoglobin is the protein in red blood cells responsible for binding oxygen; normal adult hemoglobin consists of two alpha and beta globin chains determined by the hemoglobin alpha and beta gene respectively. The modeling goal is to attain the desiderata specified above (to wit, truth conditions, inferential relationships, grading). To this end, I present a schema for the classification of point mutations and impose three modeling restrictions: The hemoglobin variants must be caused by (1) single (2) substitutions (3) at codon 6 of the hemoglobin beta gene. Finally, I briefly review why bioambient calculus, Zsyntax, and mathematical models in molecular biology are not suitable for the task at hand.

5. Simple model

In this chapter, I will introduce a simple logical model of hemoglobin variants caused by single point mutations at codon 6 of *HBB*. In section 5.1, the simple model is defined within the framework of propositional modal logic. The kind of biological modalities captured by the model are discussed in section 5.2. In section 5.3, I will make explicit how the simple model compares to normal modal logics. In section 5.4, I will show how the simple model can be made smaller via bisimulation contraction in order to facilitate its practical application. Finally, in section 5.5, I will argue that the (small) simple model allows for a distinction between active and inert silent mutations.

One way to understand the simple model is as minimal working example. The notion of a minimal working example stems from computer science and refers to the least amount of code that exactly reproduces a problem or feature of a program. Due to their reduced complexity (as compared to the corresponding full-blown programs), minimal working examples are hence heuristic devices in debugging or documenting programs. In the case at hand, the simple model is a minimal working example of models with higher degrees of freedom (such as the models presented in chapter 7) that still produces interesting results and allows for a discussion of biological modalities.

5.1 Definitions

In this chapter, I work within the framework of propositional modal logic (Blackburn et al. 2001). I start with the definition of a simple model:

Definition 5.1 (Simple model)
A simple model $\mathfrak{M}$ is a quadruple $\langle C, R, \Phi, V \rangle$ such that:

- C is the set of codons. A codon $c \in C$ is represented as string over the alphabet $\{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}$ such that $|c| = 3$.
- $R \subseteq C \times C$ is a binary relation interpreted as single substitution.
- Φ is the set of atomic propositions interpreted as the set of amino acids. The lowercase letters p, q with or without subscript range over Φ; the capital letters $\mathsf{A}, \mathsf{R}, \ldots$ denote the corresponding amino acids (including termination) as per Table 4.2.
- $V : \Phi \to \mathcal{P}(C)$ is a valuation which assigns to each atomic proposition $p \in \Phi$ some set of codons $V(p) \subseteq C$. Intuitively, the valuation indicates which codons code for which amino acids.

In a simple model, the DNA level is encoded in the frame (domain C plus binary relation R) whereas the protein level is encoded in the valuation. There is exactly one empirically adequate valuation. The empirically adequate valuation assigns to each codon the amino acid it actually codes for (see Table 4.2). Note that this empirically adequate valuation induces a partition of the set of codons C. In what follows, all other valuations will be neglected.[1] Consequently, there is exactly one empirically adequate simple model which I will call the simple model.

The graphical representation of the simple model is somewhat awkward due to its size: Its domain has $|C| = |\{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}|^{|c|} = 4^3 = 64$ elements and its substitution relation has $|R| = 576$ elements since each of the 64 codons has three positions and for each position there are three possible substitutions (recall that an empty substitution does not qualify as substitution in the biological sense). The simple model can be represented as Boolean matrix $\mathbf{B}^{\mathfrak{M}}$ (or adjacency matrix in terms of graphs) as shown in Figure 5.1. Partial simple models can be represented in the usual way as directed graphs: The nodes are given by a subset of codons and drawn as circles, the edges are given by a subset of the substitution relation and drawn as arrows. In addition, the amino acid coded for at a node is drawn in the node. Such partial representations are useful to zoom in on certain substructures of interest.

[1] This is not to say that other valuations are not logically and perhaps even physically possible.

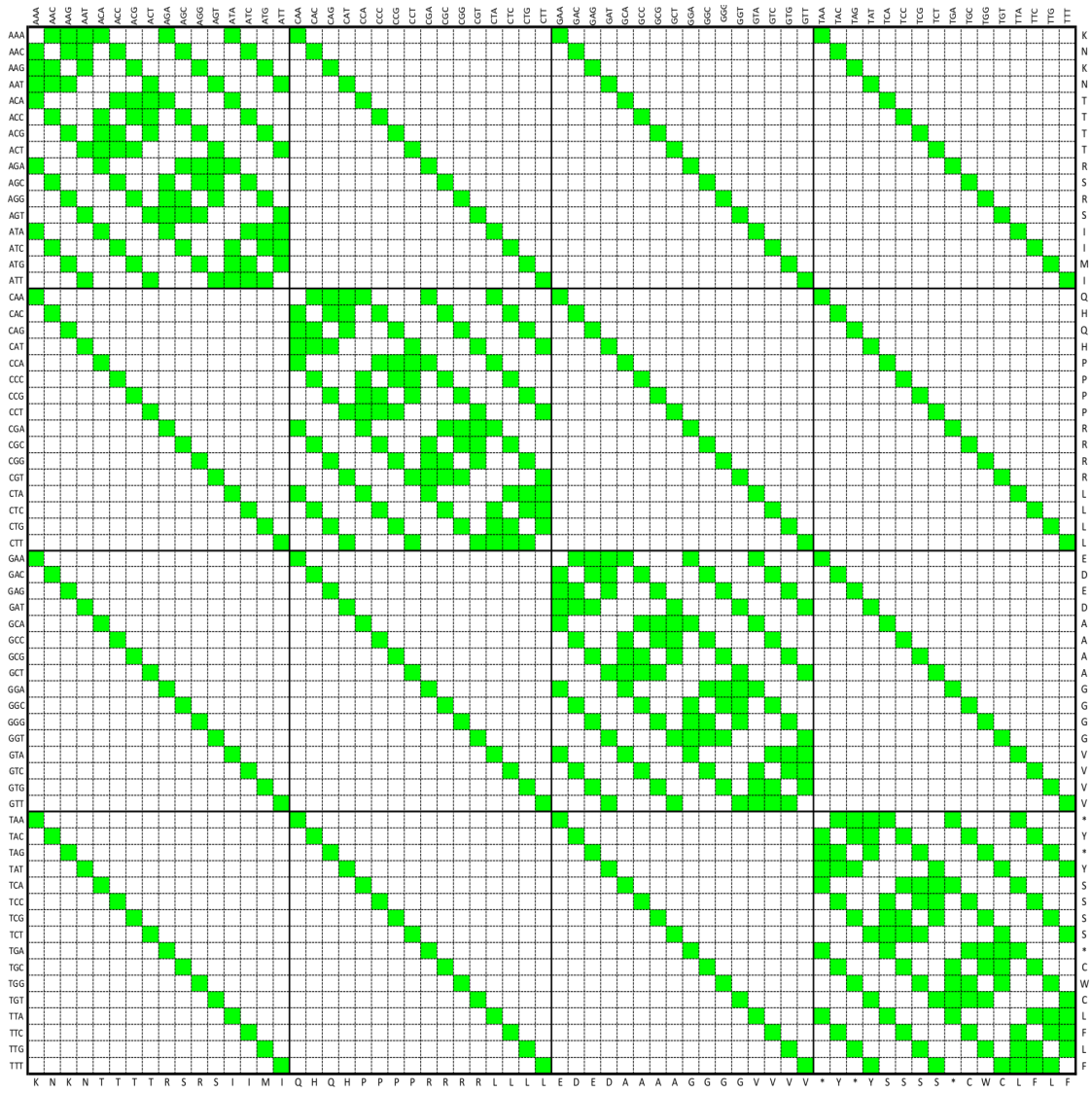


Figure 5.1

The simple model $\mathfrak{M}$ represented as Boolean matrix $\mathbf{B}^{\mathfrak{M}}$. The indices on the top and on the left are the codons in lexicographical order; the indices on the bottom and on the right are the corresponding valuations. For $\mathbf{b}_{c,c'} \in \mathbf{B}^{\mathfrak{M}}$, a green field indicates that codon c' can be reached from codon c via single substitution; a white field indicates that it cannot be reached. For example, $\mathbf{b}_{\mathtt{GAG},\mathtt{AAG}} \in \mathbf{B}^{\mathfrak{M}}$ is green, so `AAG` can be reached from `GAG` via single substitution; $\mathbf{b}_{\mathtt{GAG},\mathtt{AAA}} \in \mathbf{B}^{\mathfrak{M}}$ is white, so `AAA` cannot be reached from `GAG` via single substitution. Note that $\mathbf{B}^{\mathfrak{M}}$ is symmetric since the substitution relation is symmetric.

I now turn to the definition of the basic amino acid language:

Definition 5.2 (Basic amino acid language)
The basic amino acid language $\mathcal{L}$ is used to describe simple models $\mathfrak{M} = \langle C, R, \Phi, V \rangle$. The syntax of $\mathcal{L}$ is given by the following Backus-Naur form:

$$\phi \;:=\; p \mid \neg\phi \mid \phi \vee \phi \mid \Diamond \phi$$

where $p \in \Phi$. The standard abbreviations for the classical connectives $\wedge, \rightarrow, \leftrightarrow$ are used; in addition, it is convenient to use:

$$\Box\phi \;:=\; \neg \Diamond \neg\phi \tag{5.1}$$

$$\Diamond^n\phi := \begin{cases} \Diamond_1 \cdots \Diamond_n \phi & \text{if } n > 0 \\ \phi & \text{if } n = 0 \end{cases} \tag{5.2}$$

where $n \in \mathbb{N}$. That a formula ϕ of $\mathcal{L}$ is true in $\mathfrak{M}$ at a codon $c \in C$ is written as $\mathfrak{M}, c \Vdash \phi$. The semantics of $\mathcal{L}$ are given recursively:

$$\mathfrak{M}, c \Vdash p \text{ iff } c \in V(p) \tag{5.3}$$

$$\mathfrak{M}, c \Vdash \neg\phi \text{ iff not } \mathfrak{M}, c \Vdash \phi \tag{5.4}$$

$$\mathfrak{M}, c \Vdash \phi \vee \psi \text{ iff } \mathfrak{M}, c \Vdash \phi \text{ or } \mathfrak{M}, c \Vdash \phi \tag{5.5}$$

$$\mathfrak{M}, c \Vdash \Diamond\phi \text{ iff } \mathfrak{M}, c' \Vdash \phi \text{ for some } c' \in C \text{ such that } cRc' \tag{5.6}$$

For ease of presentation, let us call a codon at which ϕ holds a ϕ-codon. The literal meaning of $\Diamond\phi$ is that a ϕ-codon can be reached via single substitution. The intended meaning of $\Diamond\phi$ is that ϕ is possible via single substitution. The basic amino acid language $\mathcal{L}$ hence offers a reductive account of possibility via single substitution captured by the $\Diamond$-modality. Furthermore, the literal meaning of $\Diamond^n\phi$ is that a ϕ-codon can be reached via a sequence of n single substitutions. The intended meaning of $\Diamond^n\phi$ is that ϕ is possible at the n-th level via single substitution. Note that the semantics of course remain fixed of the basic amino acid language would describe simple models lacking an empirically adequate valuation.

5.2 Biological possibility

In this section, I will discuss what kind of possibility is in play here. There are at least three candidates: Logical possibility, physical possibility and biological possibility. The short answer is that the $\Diamond$-modality captures (some kind of) biological possibility. In order to give a more qualified answer, it is helpful to first consider in detail the simple model as logical model of HbA variants caused by single substitutions at codon 6 of *HBB*. I want to submit three observations:

1. When counting HbA variants caused by single substitutions at codon 6 of *HBB*, the DNA level has to be distinguished from the protein level. At the DNA level, a variant is given by a single substitution at codon 6. At the protein level, a variant is given by a change of position 6 of beta globin caused by a single substitution at codon 6. Hence the DNA level is independent from the protein level, but the inverse does not hold.

   The simple model is a logical model of HbA variants caused by single substitutions at codon 6 of *HBB* at the protein level: If $\Diamond p$ is true at codon 6, then the HbA variant where position 6 of beta globin has been changed to p is possible given codon 6. In other words, the simple model is a logical model of position 6 of beta globin caused by single substitutions at codon 6 of *HBB*. $\Diamond\mathsf{A}$, $\Diamond\mathsf{D}$, $\Diamond\mathsf{E}$, $\Diamond\mathsf{G}$, $\Diamond\mathsf{K}$, $\Diamond\mathsf{Q}$, $\Diamond\mathsf{V}$ and $\Diamond*$ are true at codon 6. Therefore, eight variants of HbA are possible: One variant for each of the amino acids A, D, E, G, K, Q, V at position 6 of beta globin; and one variant for $*$ where beta globin ends at position 6.

2. There is a discrepancy between the HbA variants predicted to be possible by the simple model and the HbA variants in the HbVar database: Only HbG-Makassar (E replaced with A), HbLavagna (E replaced with G), HbC (E replaced with K), HbMachida (E replaced with Q) and HbS (E replaced with V) are in HbVar whereas the simple model also predicts HbA variants where E is replaced with E, D and $*$. The absence of E is due to the fact that is not a variant but rather HbA, at least on the protein level. In general, there are various possible explanations for the absence of D and $*$: These variants have never been caused, or have never been observed, or are not possible contrary to the simple model.

3. The simple model is a non-specific logical model of HbA variants caused by single substitutions at codon 6 of *HBB*. That is, the simple model is a general model of variants caused by single substitutions at any codon of any gene. To see this, note

that the simple model does not encode any empirical information specific to either codon 6 or *HBB* such as upstream or downstream context. This is not to say it does not encode any empirical information; as made explicit above, the simple model is distinguished by an empirically adequate valuation from other simple models.

With these three observations in place, let us now turn to answer the question of what kind of possibility (logical, physical or biological) is captured by the $\Diamond$-modality of the basic amino acid language $\mathcal{L}$. Note that an answer to this question depends on what relationship between logical, physical and biological possibility is assumed. In section 2.2, I have argued for two uncontroversial claims with respect to the relationship between logical possibility and both physical and biological possibility: First, everything that is physically or biologically possible is also logically possible; and, second, not everything that is logically possible is also physically or biologically possible. Given these claims and neglecting complications of scope etc., the relationship between physical and biological possibility can be characterized by what I called Independence, Pluralism, Physico-Inclusivism, Bio-Inclusivism or Reductionism. Now, if for example Reductionism is assumed, then the $\Diamond$-modality trivially captures both physical and biological possibility. However, neither of Bio-Inclusivism, Reductionism and Independence is compatible with the simple model and can hence be excluded, as I will show next:

The simple model is not compatible with Bio-Inclusivism or Reductionism. Too see this, note that the substitution relation is irreflexive since a codon without a change of the type of one of its token nucleobases with respect to some wild type does not fall under the biological concept of a mutant. However, it is physically possible to replace a token nucleobase with a token nucleobase of the same type. This is an instance of PP but not BP; therefore, Bio-Inclusivism and Reductionism must be excluded. A related point can be made with respect to the fact that the set of atoms in $\mathcal{L}$ only includes proteinogenic amino acids as compared to all physically possible amino acids.

This leaves room for Independence, Pluralism and Physico-inclusivism. The general idea here is to make use of what could be called compositionality with respect to possibility: By assumption, physical and biological possibility are constructed by imposing constraints on logical possibility. Now, if biological possibility is constructed by imposing constraints on physical possibility, then Independence must be excluded. I submit that exactly this is the case: An apt albeit verbose characterization of the kind of possibility captured by the $\Diamond$-modality is the following: Logical possibility at the

protein level constrained both by biological facts about gene expression (encoded in the valuation) and by the biological concept of mutation (encoded in the binary relation).

Therefore, the $\Diamond$-modality captures biological possibility and the simple model is compatible with both Pluralism and Physico-Inclusivism. But we can go a step further. In section 2.2, I have proposed to use the factors of Scale and Historicity in order to distinguish different notions of biological possibility. In the case of the $\Diamond$-modality, the value of Scale, namely the molecular level, is already given. However, where does the $\Diamond$-modality score with respect to Historicity? In order to answer this question, it is useful to briefly recall the distinction between the local and global truth of a formula:

Definition 5.3 (Local truth)
A formula $\phi \in \mathcal{L}$ is locally true at a codon $c \in C$ in the simple model $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ if and only if $\mathfrak{M}, c \Vdash \phi$.

So the semantic clauses of $\mathcal{L}$ as per definition 5.2 are all phrased in terms of local truth. Based on local truth, global truth (or model truth) can be defined:

Definition 5.4 (Global truth)
A formula $\phi \in \mathcal{L}$ is globally true in the simple model $\mathfrak{M} = \langle C, R, \Phi, V \rangle$, written as $\mathfrak{M} \Vdash \phi$, if and only if ϕ is locally true at all $c \in C$.

By the same token, validity can be defined based on global truth as global truth in all models.[2] The difference between local and global truth is one of perspective (Blackburn et al. 2001: 18). So when we say that a formula is locally true we take the perspective of a codon; by contrast, when we say that a formula is globally true we take the perspective of the simple model. Now, I propose to cash out the difference between historical and ahistorical biological possibility by adopting exactly this bifurcation of perspectives. We can then define historical and ahistorical biological possibility along the following lines:

Definition 5.5 (Historical biological possibility)
A formula $\phi \in \mathcal{L}$ is HB-possible at a codon $c \in C$ in the simple model $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ if and only if $\mathfrak{M}, c' \Vdash \phi$ for some $c' \in C$ such that cRc'.

Definition 5.5 states that historical biological possibility is captured by the $\Diamond$-modality.

[2] The notion of the validity of a formula (as compared to validity tout court) does not apply here since we have fixed the valuation of the simple model; global truth and validity hence coincide with respect to the simple model.

Contrast this with ahistorical biological possibility:

Definition 5.6 (Ahistorical biological possibility)
A formula $\phi \in \mathcal{L}$ is AB-possible in a model $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ if and only if $\mathfrak{M}, c \Vdash \phi$ for some $c \in C$.

In short, in the simple model, historical biological possibility is relativized to a codon whereas ahistorical biological possibility is relativized to the simple model itself. Note that definition 5.6 provides a weak notion of historical biological possibility. By this I mean that the only thing that makes definition 5.6 historical is that it takes a local perspective. Stronger versions can implemented by extending the simple model as to add further constraints. For example, recall the example of the cost function that privileges words in the English Oxford Dictionary as intermediates in an edit script over random strings discussed in section 3.4); constraints such as viability or certain functional properties could be implemented in an analogous manner.

5.3 Simple model logic

The basic amino acid language gives rise to the normal modal logic **KDBC4** which is sound and complete with respect the the class of serial, symmetric and dense relational structures of which the simple model is an instance (see appendix C. for details). Here I will briefly show that the single biological substitution relation is serial, symmetric and dense, and briefly comment on the corresponding axioms.

The single biological substitution relation is serial. That is, for each codon $c \in C$, there exists a codon $c' \in C$ such that cRc'. Informally, this means that each codon is prone to single substitution. Therefore, the D-axiom holds in the simple model:

$$\mathfrak{M} \Vdash \Box\phi \rightarrow \Diamond\phi \tag{5.7}$$

The single biological substitution relation is symmetric. That is, for all codons $c, c' \in C$, if cRc', then $c'Rc$. Informally, this means that a single substitution on a codon can be reversed. Therefore, the B-axiom holds in the simple model:

$$\mathfrak{M} \Vdash \phi \rightarrow \Box \Diamond \phi \tag{5.8}$$

The single biological substitution relation is dense. That is, for all codons $c, c' \in C$, if

cRc', then there exists a codon $c'' \in C$ such that cRc'' and $c''Rc'$. Informally, this means that a single substitution can be extended into into a sequence of single substitutions. Therefore, the C4-axiom holds in the simple model:

$$\mathfrak{M} \Vdash \Diamond\phi \rightarrow \Diamond^2\phi \tag{5.9}$$

Two observations are important. First, these axioms hold also for simple models without empirically adequate valuation. Second, what to make of the axioms (5.7)–(5.9)? Given the intended meaning of the $\Diamond$-operator as biological possibility via single substitution, (5.7) states that biological possibility implies biological possibility. So whatever HbA variant is biologically necessary is also biologically possible. (5.8) states that whatever HbA variant is actual is such that it being biologically possible is biologically necessary. Put differently, an actual HbA variant that is biologically impossible is biologically impossible. (5.9) states that biological possibility implies biological possibility at the second level. So whatever HbA variant is biologically possible is also biologically possible in a less direct way or sense.

5.4 Small simple model

Even though the simple model is much smaller than the Library of Mendel (see section 3.3.1), it is still rather large for what concerns its practical application. However, it can be made smaller by bisimulation contraction (see Blackburn and van Benthem 2007): Take the bisimilarity class of each codon in the simple model and construct a new model by relating the bisimilarity classes if some of their members are related via single substitution in the simple model. For this recall the definition of a bisimilarity class:

Definition 5.7 (Bisimilarity class)
The bisimilarity class of a codon $c \in C$ in a simple model $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ is the set $\{c' : \mathfrak{M}, c \leftrightarrows \mathfrak{M}, c'\}$ and written as $\|c\|$.

Bisimilarity classes are in turn based on the definition of bisimulation:

Definition 5.8 (Bisimulation)
$Z \subseteq C \times C'$ is a bisimulation between two simple models $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ and $\mathfrak{M}' = \langle C', R', \Phi', V' \rangle$ iff for $c \in C$ and $c' \in C'$:

- If cZc', then c and c' share a valuation, and
- if cZc' and cRx, then there is a $x' \in C'$ such that xZx' and $c'R'x'$, and
- if cZc' and $c'R'x'$, then there is a $x \in C$ such that xZx' and cRx.

Two simple models $\mathfrak{M}, \mathfrak{M}'$ or two states c, c' are bisimilar, written as $\mathfrak{M} \leftrightarrows \mathfrak{M}'$ respectively as $\mathfrak{M}, c \leftrightarrows \mathfrak{M}', c'$, if there is a bisimulation between them.

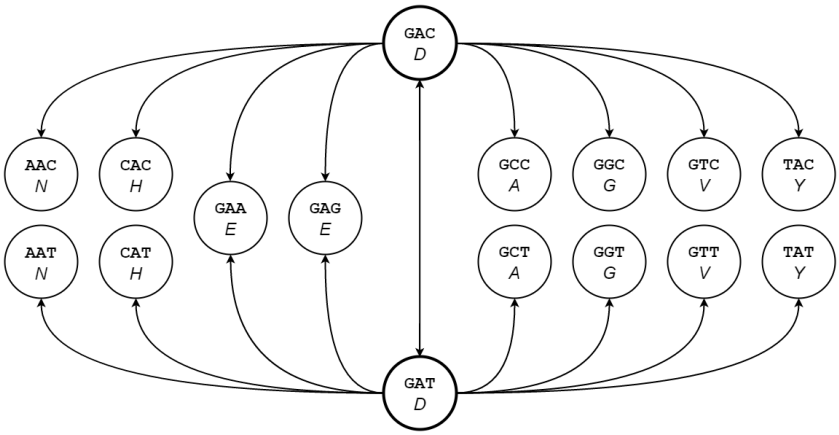
Intuitively, the bisimilarity class of a codon is constituted by the codons that code for the same amino acid and exactly match the types of codons that can be reached via single substitution in the simple model. For example, there are two distinct D-codons reachable from codon 6 via single substitution that are bisimilar as detailed in Figure 5.2.

Consider now the definition of the small simple model based on the simple model $\mathfrak{M} = \langle C, R, \Phi, V \rangle$:

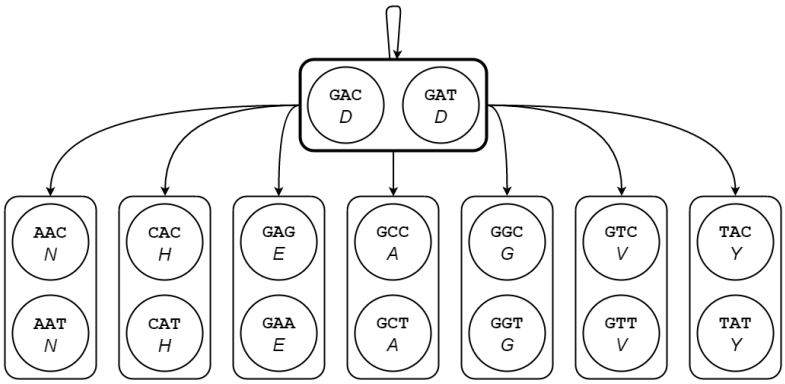
Definition 5.9 (Small simple model)
The small simple model $\mathfrak{S}$ is a quadruple $\left\langle C^{\mathfrak{S}}, R^{\mathfrak{S}}, \Phi^{\mathfrak{S}}, V^{\mathfrak{S}} \right\rangle$ where:

- $C^{\mathfrak{S}}$ is the set of bisimilarity classes $\|c\|$ of codons $c \in C$.
- $R^{\mathfrak{S}} \subseteq C^{\mathfrak{S}} \times C^{\mathfrak{S}}$ is a binary relation such that $\|c\| R^{\mathfrak{S}} \|c'\|$ if there are $c \in \|c\|$ and $c' \in \|c'\|$ such that cRc'.
- $\Phi^{\mathfrak{S}} = \Phi$.
- $V^{\mathfrak{S}} : \Phi^{\mathfrak{S}} \to C^{\mathfrak{S}}$ is a valuation function such that $\|c\| \in V^{\mathfrak{S}}(p)$ if $c \in V(p)$.

The small simple model can be represented as Boolen matrix $\mathbf{B}^{\mathfrak{S}}$ as shown in Figure 5.3. By construction, the simple model and the small simple model are bisimilar. Since basic modal formulas of are invariant for bisimulation (Hennessy-Milner Theorem, see Hennessy and Milner 1985), each codon and its respective bisimilarity class satisfy the same formulas of the basic amino acid language $\mathcal{L}$. For the purpose of discussion, we can hence trade in the simple model for the less complex small simple model without loss of generality.



(a) Partial simple model $\mathfrak{M}$



(b) Partial small simple model $\mathfrak{S}$

Figure 5.2

Codons that can be reached from GAC, GAT (bold circles) in the simple model before and after bisimilarity contraction (bisimilarity classes are drawn as rectangles). GAC and GAT are bisimilar since they code for the same amino acid and for each p-codon that can be reached from GAC via single substitution, there is a p-codon that can be reached from GAT via single substitution (and vice versa). Therefore GAC and GAT constitute a bisimilarity class in the small simple model (bold rectangle).

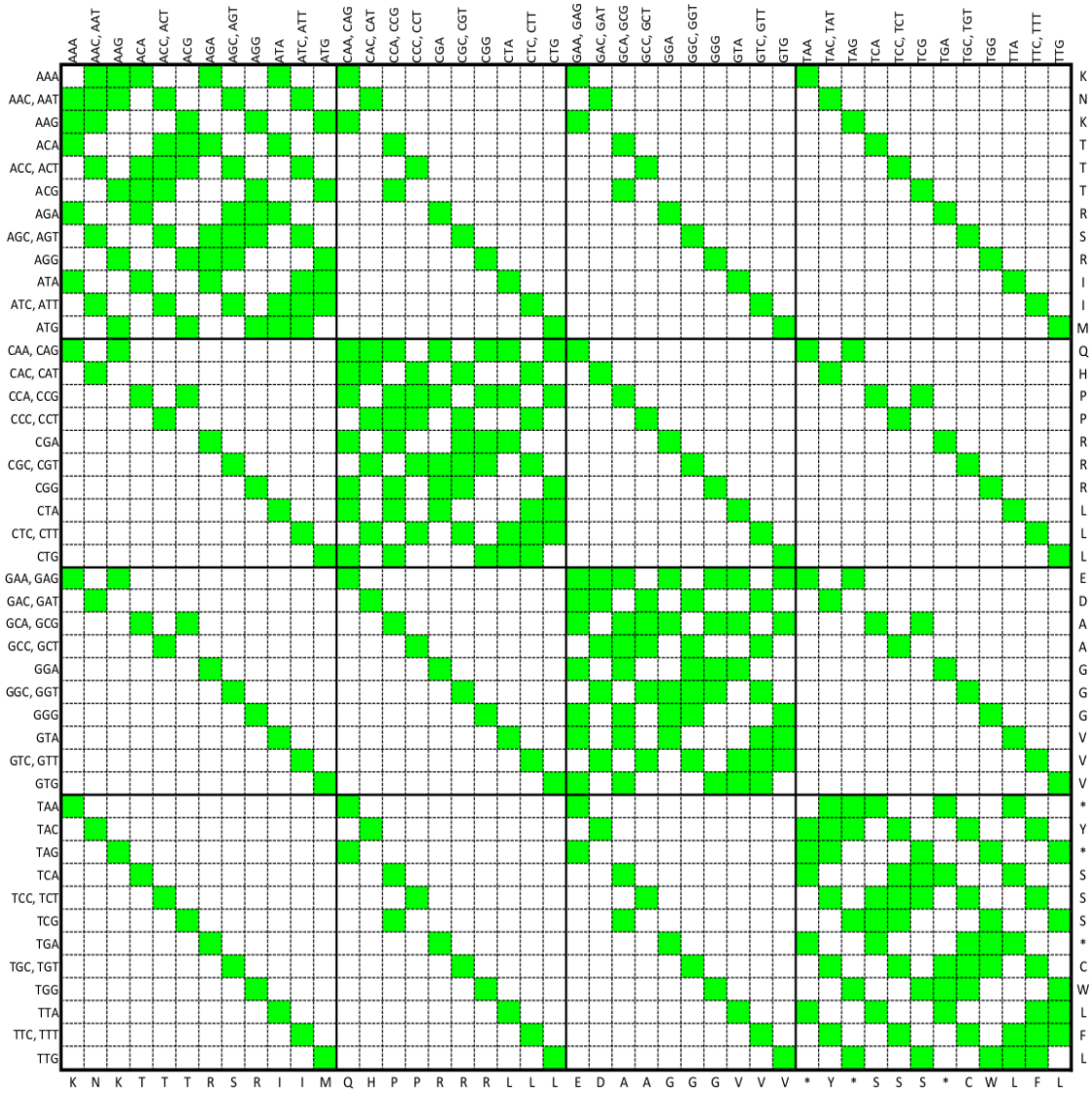


Figure 5.3

The small simple model $\mathfrak{S}$ represented as Boolean matrix $\mathbf{B}^{\mathfrak{S}}$. The rows and columns are the bisimilarity classes in lexicographical order. The indices on the top and on the left are the codons in lexicographical order; the indices on the bottom and on the right are the corresponding valuations. For $\mathbf{b}_{\|c\|,\|c'\|} \in \mathbf{B}^{\mathfrak{S}}$, a green field indicates that the bisimilarity class $\|c'\|$ can be reached from the bisimilarity class $\|c\|$ via single substitution; a white field indicates that it cannot be reached. For example, $\mathbf{b}_{\|\mathtt{GAG}\|,\|\mathtt{AAG}\|} \in \mathbf{B}^{\mathfrak{S}}$ is green, so $\|\mathtt{AAG}\|$ can be reached from $\|\mathtt{GAG}\|$ via single substitution; $\mathbf{b}_{\|\mathtt{GAG}\|,\|\mathtt{AAA}\|} \in \mathbf{B}^{\mathfrak{S}}$ is white, so $\|\mathtt{AAA}\|$ cannot be reached from $\|\mathtt{GAG}\|$ via single substitution. Again, $\mathbf{B}^{\mathfrak{S}}$ is symmetric since the substitution relation is symmetric.

5.5 Active versus inert silent mutations

In the small simple model, there are 44 bisimilarity classes: 24 singleton bisimilarity classes and 20 bisimilarity classes with two members. I will now consider these bisimilarity classes in more detail; this will allow me to introduce the distinction between active and inert silent mutations. At the DNA level, for $c, c' \in \|c\|$ where $c \neq c'$, c is a transition at the third position with respect to c' (and vice versa since transitions are symmetric); and, at the protein level, c is a silent mutation of c' (and vice versa since silent mutations are symmetric). That is, each member of a non-singleton bisimilarity class is a transition/silent mutation at the third position with respect to the other member of that class. For example, codon 6 of *HBB*, `GAG`, and `GAA` are in a bisimilarity class, hence `GAG` is a transition/silent mutation at the third position with respect to `GAA` (and vice versa).

However, not all sets of codons where each member is a transition at the third position with respect to the other members of that set are such that they constitute a bisimilarity class. For example, `ATA` is a transition at the third position with respect to `AAG` (and vice versa), but `ATA` codes for I whereas `ATG` codes for $*$; so `ATA` and `ATG` are not bisimilar. More importantly, not all sets of codons where each member is a silent mutation at the third position with respect to the other members of that set are such that they constitute a bisimilarity class. For example, `AAA` is silent mutation at the third position with respect to `AAG` (and vice versa), but `AAA` can reach an I-codon via single substitution whereas `AAA` cannot; so `AAG` and `AAA` are not bisimilar.

Figuratively speaking, this means that some silent mutations make modal noise whereas others do not: If the mutant caused by a silent mutation is not bisimilar to the wild type, the possible HbA variants for the mutant differ from the possible HbA variants for the wild type (despite the mutant coding for the same amino acid as the wild type). I hence propose to append the classification of point mutations given by Figure 4.2 as follows: Call a silent mutation 'inert' if the mutant and the wild type are bisimilar, and 'active' otherwise. In contrast to inert silent mutations, active silent mutations impact fitness. For example, take `TCC` which codes for serine S and consider two distinct silent mutations at the third position, namely the active silent mutation `TCC` $\rightsquigarrow$ `A` resulting in

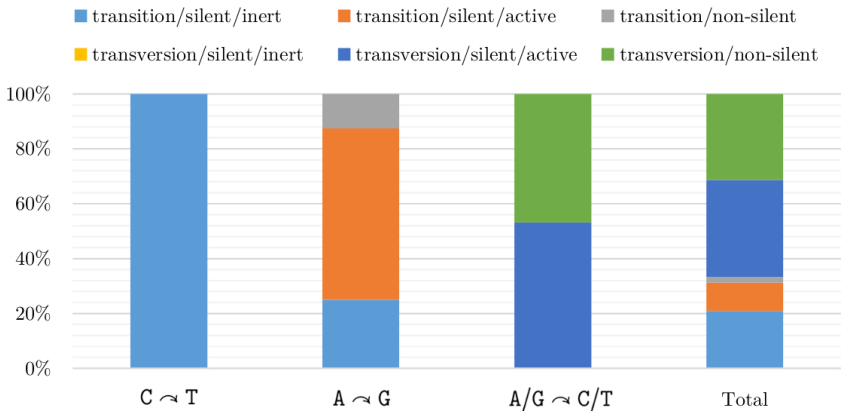


Figure 5.4
Distribution of inert and active silent mutations over the third position of all codons in the (small) simple model.

TCA, and the inert silent mutation TCC ⇝ T resulting in TCT. It now holds:

$$\mathfrak{M}, \texttt{TCA} \Vdash \Diamond * \tag{5.10}$$

$$\mathfrak{M}, \texttt{TCT} \nVdash \Diamond * \tag{5.11}$$

That is, a single substitution resulting in termination $*$ (or nonsense mutation in short) is biologically possible at TCA but not at TCT. Therefore, the active silent mutation but not the inert silent mutation impacts the possible variants of TCC hence providing the basis for an impact on fitness.[3] To illustrate, simply consider the weak assumption that a nonsense mutation has a stronger impact on fitness than other classes of point mutations. Note that the framework provided in chapter 6 provides the tools to quantify the first kind of impact.

I turn now to the distribution of inert and active silent mutations in the (small) simple model as summarized in Figure 5.4. A preliminary observation is that only single substitutions at the third position of each codon need to be considered; single substitutions at other positions are never inert silent mutations. Consider first the transitions: All C ⇝ T transitions at the third position are inert silent mutations. By contrast, only 25% of all A ⇝ G transitions at the third position are inert silent mutations (CAA ⇝ G, CCA ⇝ G, GAA ⇝ G, GCA ⇝ G); 62.5% are active silent mutations (AAA ⇝ G, ACA ⇝ G, AGA ⇝ G, CGA ⇝ G, CTA ⇝ G, GGA ⇝ G, GTA ⇝ G, TAA ⇝ G, TCA ⇝ G,

[3] This distinction can also be cashed out in terms of dispositions, counterfactual stability, robustness, modal probabilies, and son.

TTA $\rightsquigarrow$ G); and 12.5% are non-silent mutations (ATA $\rightsquigarrow$ G, TGA $\rightsquigarrow$ G). And second, the transversions: 53.12% of the transversions at the third position are active silent mutations (AAA/G $\rightsquigarrow$ C/T, ATA $\rightsquigarrow$ C/T, CCA/G $\rightsquigarrow$ C/T, CGA/G $\rightsquigarrow$ C/T, CTA/G $\rightsquigarrow$ C/T, GCA/G $\rightsquigarrow$ C/T, GGA/G $\rightsquigarrow$ C/T, GTA/G $\rightsquigarrow$ C/T, TCA/G $\rightsquigarrow$ C/T); 46.88% are non-silent mutations (ACA/G $\rightsquigarrow$ C/T, AGA/G $\rightsquigarrow$ C/T, ATG $\rightsquigarrow$ C/T, CAA/G $\rightsquigarrow$ C/T, GAA/G $\rightsquigarrow$ C/T, TAA/G $\rightsquigarrow$ C/T, TGA/G $\rightsquigarrow$ C/T, TTA/G $\rightsquigarrow$ C/T); and none of them are inert silent mutations.

5.6 Summary

I introduce a simple model of hemoglobin variants caused by single substitutions at codon 6 of the hemoglobin beta gene within the framework of propositional modal logic. In the model, states are interpreted as codons, the binary relation is interpreted as single substitution, and the valuation is kept fixed and induces a partition of blocks of codons that code for some amino acid. I argue that explicit truth conditions for at least historical and ahistorical biological modalities are attained via the modal language describing the model. This gives rise to a normal modal logic that is sound and complete with respect to the class of serial, symmetric and dense frames. After showing that the model can be simplified via bisimulation contraction, I argue that the notion of silent mutation is ambiguous between mutants that are bisimilar to the wild type and hence modally inert, and mutants that are not and hence modally active.

6. Graded models

In this chapter, I will be concerned with grading biological possibility. As explained in section 2.2, the idea of grading possibility is somewhat ambiguous. Here I will focus on what I called comparative biological possibility, namely determining a ranking for the possibilities within one kind of biological possibility. More precisely, I will focus on the ranking of possible HbA variants caused by single substitutions at codon 6 of *HBB*. That is, for two HbA variants v, v', the task is to spell out under what circumstances v is more possible than v'. For this, it is useful to distinguish two stages of modeling, namely the conceptual stage and the stage of implementation.

First, at the conceptual stage, the intended meaning for the 'more possible' locution must be fixed. Here I will consider four ways to do so:

1. Simplicity: v is more possible than v' iff it is more easy to bring about v than v'
2. Quantity: v is more possible than v' iff there are more possible v than v'
3. Process: v is more possible than v' iff there are more ways to realize v than v'
4. Probability: v is more possible than v' iff v is more probable than v'

A couple of remarks are in order. Simplicity depends of course on how exactly 'more easy' is defined. What I intend here is in line with definition 3.27 of a string editing problem: v is more easy to bring about than v' iff the least costly edit script from (say) the wild type to v is less costly than the least costly edit script from the wild type to v'. Probability is in effect a reduction of comparative possibility to probability. Similar to Simplicity, Probability depends on how exactly 'more probable' is defined. I submit that the probabilistic model discussed below is open to various interpretations of probability; the most detailed example employing an amino acid scoring matrix based probability function relies on a frequentist interpretation of probability. In contrast to Simplicity and Probability, the interpretation of Quantity is straightforward:

Whether there are more possible v than v' can be counted in the model. The same holds for Process: There are more ways to realize v than v' iff there are more unique paths to v than to v' in the model (that is, the relevant pairs in the binary relation are counted).

Second, at the level of implementation, the simple model or the basic amino acid language is changed as to reflect the choice at the conceptual stage. Note that the availability of technical tools at the implementation stage somewhat constrains the conceptual stage. There are at least three available techniques to change the simple model or the basic amino acid language in order to implement graded modalities (see Legastelois et al. 2015 for a general overview): Count the codons that are reachable via the substitution relation, use a weighted substition relation, or use weighted codons. In what follows, some of these techniques or extensions thereof will be applied to implement Simplicity, Quantity, Process and Probability.

In section 6.1, Simplicity is implemented as Hamming distance whilst keeping the simple model and the basic amino acid language fixed. In section 6.2, Quantity and Process are implemented by keeping the simple model fixed but changing the basic amino language such that codons and unique sequences of substitutions can be counted. In section 6.3, Probability is implemented by changing both the simple model and the basic amino acid language. The upshot of each section is a ranking of the possible HbA variants caused by single substitutions at codon 6 of *HBB*.

6.1 Simplicity

The basic amino acid language $\mathcal{L}$ is not suitable to implement any of Quantity, Process or Probability. However, Simplicity can be implemented via the $\Diamond^n$-modality of $\mathcal{L}$. The $\Diamond^n$-modality allows for what I called levels of possibility. For example, $\Diamond^1\mathsf{A}$, $\Diamond^2\mathsf{H}$ and $\Diamond^3\mathsf{C}$ are true at codon 6 of *HBB*; the literal meaning is that A, H and C can be reached via single substitution, via two subsequent single substitutions, and via three subsequent single substitutions respectively. The intended meaning is that A, H and C are possible, possible to the second level, and possible to the third level respectively; more precisely, that HbA variants where position 6 of beta globin has been changed to A, H and C are are possible, possible to the second level, and possible to the third level respectively. These levels of possibility can be understood as a measure of how easy it is to bring about a certain HbA variant via single substitution. As mentioned above, Simplicity allows for many different implementations depending on the exact criterion

for what counts as easy; here the criterion is 'the less substitutions, the easier'. Consider introducing the following abbreviation to express this in $\mathcal{L}$ (for $i, j \in \mathbb{N}$):

$$\phi >_{\Diamond} \psi := \Diamond^i \phi \wedge \Diamond^j \psi \text{ and } i < j \tag{6.1}$$

The literal meaning of $\phi >_{\Diamond} \psi$, in line with SIMPLICITY, is that a ϕ-codon can be reached with fewer single substitutions than a ψ-codon; the intended meaning is that ϕ is more possible than ψ. However, (6.1) leads to contradictions or at least gibberish. For example, A is more possible than H at codon 6 since $\Diamond^1\mathsf{A} \wedge \Diamond^2\mathsf{H}$ is true at codon 6 and $1 < 2$. But H is more possible than A at codon 6 since $\Diamond^2\mathsf{H} \wedge \Diamond^3\mathsf{A}$ is true at codon 6 and $2 < 3$; so H is more possible than A and A is more possible than H. More generally, when using the $\Diamond^n$-modality for grading, two limitations need to be observed:

First, it holds that:

$$\text{If } n \geq 3, \text{ then } \mathfrak{M} \Vdash \Diamond^n \phi \rightarrow \Diamond^3 \phi \vee \Diamond^2 \phi \vee \Diamond^1 \phi \vee \phi \tag{6.2}$$

That is, the $\Diamond^n$ modality bottoms out at the third level in the simple model. To see this, note that the substitution relation can be used to compute the Hamming distance between codons (see chapter 3). The Hamming distance is the number of positions at which two strings of equal length do not have the same symbol. The simple model encodes codons as strings and the substitution relation between two codons c and c' holds if and only if the Hamming distance between c and c' equals 1. By counting the number of substitutions required to connect two arbitrary codons in the simple model, the Hamming distances in the simple model can be computed as shown in Figure 6.1. Now, if $\mathfrak{M}, c \Vdash \Diamond^n \phi$, then there is a c' and a sequence of substitutions $cR_1, \ldots, R_n c'$ such that $\mathfrak{M}, c' \Vdash \phi$. But since the maximal Hamming distance between c and c' has a lower limit of 0 and an upper limit of 3, either $c = c'$, or there is a sequence of substitutions $cR_1, \ldots, R_i c'$ where $1 \leq i \leq 3$. Therefore, $\mathfrak{M}, c \Vdash \Diamond^3 \phi \vee \Diamond^2 \phi \vee \Diamond^1 \phi \vee \phi$.

And second, $\mathfrak{M}, c \Vdash \Diamond^n \phi$ for $0 \leq n \leq 3$ does not correspond to a Hamming distance of n between c and a ϕ-codon. One reason for this is that the substitution relation is symmetric.

Given these limitations, the $\Diamond^n$-modality can be used to construct a Hamming distance operator that suits the purpose of grading possibility in line with SIMPLICITY. In the simple model, the Hamming distance between c and a p-codon is given by taking minimum of $\{n : \mathfrak{M}, c \Vdash \Diamond^n p\}$ as shown in Figure 6.2. In $\mathcal{L}$, this can be expressed by

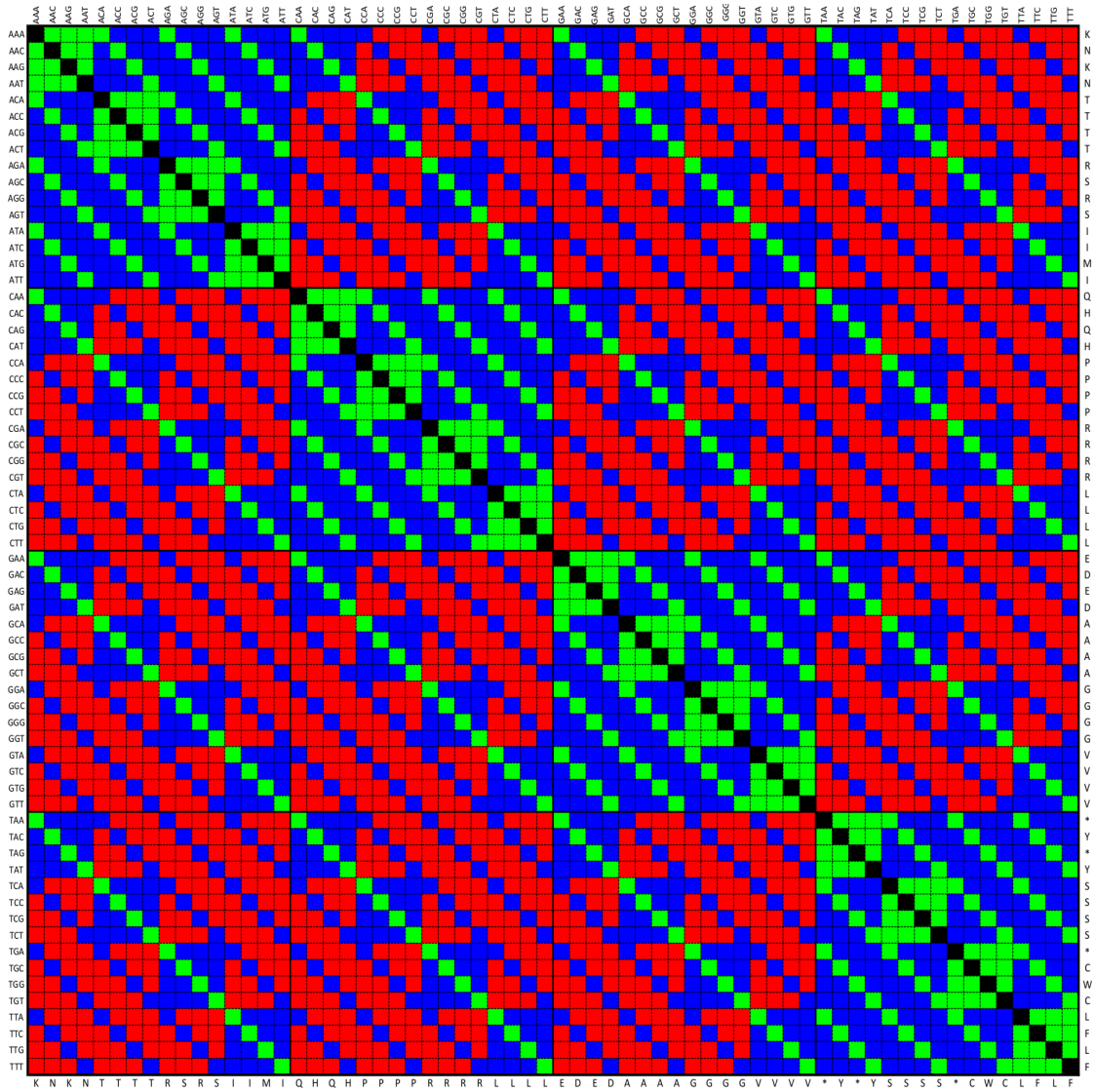


Figure 6.1

Hamming distances in the simple model $\mathfrak{M}$ represented as matrix $\mathbf{H}^{\mathfrak{M}}$. The indices on the top and on the left are the codons in lexicographical order; the indices on the bottom and on the right give the valuation. For $\mathbf{h}_{c,c'} \in \mathbf{H}^{\mathfrak{M}}$, a black, green, blue or red field indicates a Hamming distance of 0, 1, 2 or 3 respectively. For example, $\mathbf{h}_{\mathtt{GAG},\mathtt{AAA}}$ is blue, so the Hamming distance between `GAG` and `AAA` is 2. Note that $\mathbf{H}^{\mathfrak{M}}$ is symmetric.

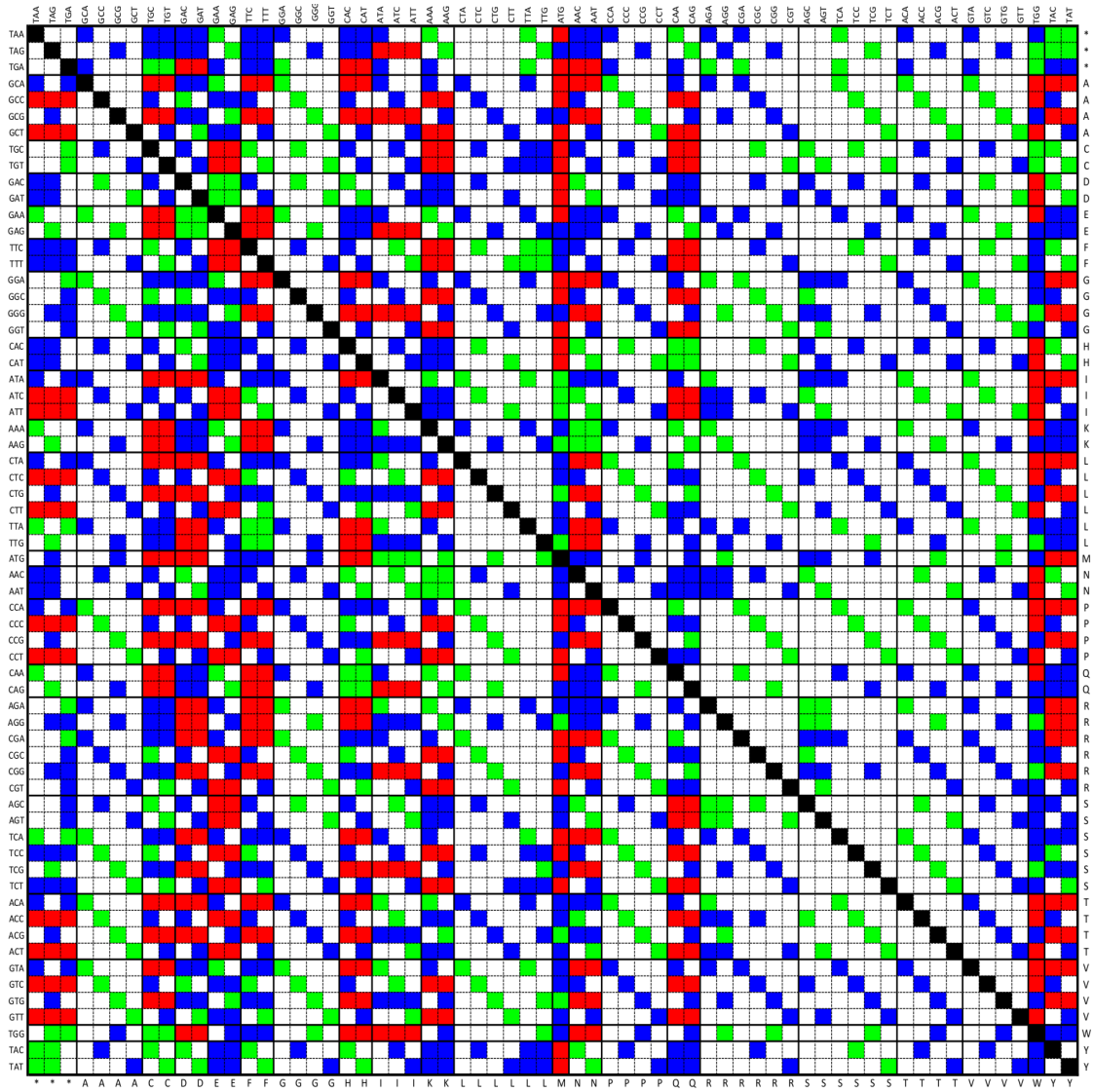


Figure 6.2

Minimum Hamming distances between codons and amino acids in the simple model $\mathfrak{M}$ represented as matrix $\mathbf{M}^{\mathfrak{M}}$. The indices on the top and on the left are the codons which are arranged in blocks B according to the partition induced by the valuation $(\forall B \exists! p V(p) = B)$, separated by bold lines, in lexicographical order of the valuation which is given by the indices on the bottom and the right. For $\mathbf{m}_{c,B} \in \mathbf{M}^{\mathfrak{M}}$ colored fields indicate the codon(s) $c' \in B$ such that the Hamming distance between c and c' is minimized with respect to B. Black, green, blue and red fields indicate a minimum Hamming distance of 0, 1, 2, or 3 respectively. For example, $\mathbf{m}_{\mathtt{GAG},*}$ is green, so the minimum Hamming distance between `GAG` and the $*$-block is 1. Note that $\mathbf{M}^{\mathfrak{M}}$ is not symmetric.

introducing the following abbreviations (for $n, i, j \in \mathbb{N}$):

$$\mathrm{H}^n\phi := \Diamond^n\phi \wedge \neg \Diamond^{n-1} \phi \wedge \cdots \wedge \neg \Diamond^0 \phi \tag{6.3}$$

$$\phi >_{\mathrm{H}} \psi := \mathrm{H}^i\phi \wedge \mathrm{H}^j\psi \text{ and } i < j \tag{6.4}$$

$\mathrm{H}^n\phi$ expresses that the Hamming distance to a ϕ-codon is n. The literal meaning of $\phi >_{\mathrm{H}} \psi$ is that the Hamming distance to a ϕ-codon is smaller than the Hamming distance to a ψ-codon; the intended meaning is that ϕ is more possible than ψ. Returning to the above example, $\mathrm{H}^1\mathsf{A}$, $\mathrm{H}^2\mathsf{H}$ and $\mathrm{H}^3\mathsf{C}$ are true at codon 6, so A is more possible than H and H is more possible than C (and A is more possible than H). Abusing the notation, this yields the following full ranking of possible HbA variants caused by single substitutions at codon 6 of *HBB*:

$$\mathfrak{M}, \mathtt{GAG} \Vdash \mathsf{E} >_{\mathrm{H}} *, \mathsf{A}, \mathsf{D}, \mathsf{G}, \mathsf{K}, \mathsf{Q}, \mathsf{V} >_{\mathrm{H}} \mathsf{H}, \mathsf{L}, \mathsf{M}, \mathsf{N}, \mathsf{P}, \mathsf{R}, \mathsf{S}, \mathsf{T}, \mathsf{W}, \mathsf{Y} >_{\mathrm{H}} \mathsf{C}, \mathsf{F}, \mathsf{I} \tag{6.5}$$

6.2 Quantity and process

The idea of counting accessible states in order to attain graded modalities was introduced by Goble (1970) and Fine (1972); it has since then been refined by various authors. In what follows, I will extend the standard framework of graded modal logic as presented by Pacuit and Salame (2004) in two directions: First, in addition to a modality that counts accessible codons, a modality that counts unique sequences of single substitutions is introduced. Second, these modalities are allowed to look farther than at a single substitution. This will enable me to implement both Quantity and Process. I start by defining the counting amino acid language:

Definition 6.1 (Counting amino acid language)
The counting amino acid language $\mathcal{L}^{\mathcal{C}}$ is used to describe simple models $\mathfrak{M} = \langle C, R, \Phi, V \rangle$. The syntax of $\mathcal{L}^{\mathcal{C}}$ is given by the following Backus-Naur form:

$$\phi \;:=\; p \mid \neg\phi \mid \phi \vee \phi \mid \delta^m_n\phi$$

where $p \in \Phi$, $\delta \in \{\Diamond, \diamondsuit\}$ and $m, n \in \mathbb{N}$. The standard abbreviations for the classical

connectives $\wedge, \rightarrow, \leftrightarrow$ are used; in addition, it is convenient to use:

$$\beta_n^m\phi := \begin{cases} \neg \Diamond_n^m \neg\phi & \text{if } \beta = \Box \\ \neg \diamondsuit_n^m \neg\phi & \text{if } \beta = \boxdot \end{cases} \tag{6.6}$$

$$\delta_n^0\phi := \phi \tag{6.7}$$

$$\delta_0^m\phi := \delta^m\phi \tag{6.8}$$

$$\delta!_n^m\phi := \begin{cases} \delta_{n-1}^m\phi \wedge \neg\delta!_n^m\phi & \text{if } n > 0 \\ \neg\delta^m & \text{if } n = 0 \end{cases} \tag{6.9}$$

$$\phi >_\delta^m \psi := \delta!_i^m\phi \wedge \delta!_j^m\psi \text{ and } i > j \tag{6.10}$$

$$\phi \rhd_\delta^m \psi := \bigwedge_{k=1}^{m} (\delta!_{i_k}^k \wedge \delta!_{j_k}^k) \text{ and } \sum_{k=1}^{m} i_k > \sum_{k=1}^{m} j_k \tag{6.11}$$

where $i, j \in \mathbb{N}$. The semantics of $\mathcal{L}^{\mathcal{C}}$ are identical to $\mathcal{L}$ as per definition 5.2 for non-modal formulas. The semantics for the modal operators are:

$$\mathfrak{M}, c \Vdash \delta_n^m\phi \text{ iff } \begin{cases} |\{c' : cR_1 \dots R_m c' \text{ and } \mathfrak{M}, c' \Vdash \phi\}| > n & \text{if } \delta = \Diamond \\ |\{\langle c, \dots, c'\rangle : cR_1 \dots R_m c' \text{ and } \mathfrak{M}, c' \Vdash \phi\}| > n & \text{if } \delta = \diamondsuit \end{cases} \tag{6.12}$$

The $\Diamond_n^m$-modality combines the 'true in at least $n+1$ states from here' $\Diamond_n$-modality with the 'true somewhere m steps from here' $\Diamond^m$-modality. $\Diamond_n^m\phi$ expresses that at least $n+1$ ϕ-codons can be reached via a sequence of m single substitutions; $\Box_n^m\phi$ expresses that ϕ does not hold at all but n codons that can be reached via a sequence of m single substitutions; and $\Diamond!_n^m\phi$ expresses that exactly n ϕ-codons can be reached via a sequence of m single substitutions. The literal meaning of $\phi >_\Diamond^m \psi$ is that more ϕ-codons than ψ-codons can be reached via a sequence of m single substitutions; the intended meaning, in line with Quantity, is that ϕ is more possible than ψ within a level of possibility m. The literal meaning of $\phi \rhd_\Diamond^m \psi$ is that more ϕ-codons than ψ-codons can be reached via the union of sequences of $1, \dots, m$ single substitutions; the intended meaning, in line with Quantity, is that ϕ is more possible than ψ across the levels of possibility $1, \dots, m$.

While the $\Diamond_n^m$-modality counts codons, the $\diamondsuit_n^m$-modality counts unique sequences of single substitutions: $\diamondsuit_n^m\phi$ expresses that some ϕ-codon(s) can be reached via at least $n+1$ unique sequences of m single substitutions; $\boxdot_n^m\phi$ expresses that ϕ does not hold at some codon(s) that can be reached via all but n unique sequences of m single substitutions; and

$\diamondsuit!_n^m\phi$ expresses that some ϕ-codon(s) can be reached via at exactly n unique sequences of m single substitutions. The literal meaning of $\phi >_\diamondsuit^m \psi$ is that there are more unique sequences of m single substitutions to reach some ϕ-codon(s) than there are unique sequences of m single substitutions to reach some ψ-codon(s); the intended meaning, in line with PROCESS, is that ϕ is more possible than ψ within a level of possibility m. The literal meaning of $\phi \rhd_\diamondsuit^m \psi$ is that there are more unique sequences of $1, \ldots, m$ unique single substitutions to reach some ϕ-codon(s) than there are unique sequences of $1, \ldots, m$ single substitutions to reach some ψ-codon(s); the intended meaning, in line with PROCESS, is that ϕ is more possible than ψ across the levels of possibility $1, \ldots, m$.

In what follows, I will spell out the grading of HbA variants caused by single substitutions at codon 6 of *HBB* in terms of these implementations of QUANTITY and PROCESS. Here the notion of the global grading Γ will be useful as limit for the loss of local context of the evaluation codon. Put differently, Γ indicates an ahistorical grading of HbA variants. Γ is given by an ordering according to the size of the blocks in the partition of the set of codons induced by the valuation in the simple model $\mathfrak{M} = \langle C, R, \Phi, V \rangle$; in other words, Γ is given by an ordering of the fraction of p-codons:

$$\Gamma = \mathsf{L}, \mathsf{R}, \mathsf{S} >_\gamma \mathsf{A}, \mathsf{G}, \mathsf{P}, \mathsf{T}, \mathsf{V} >_\gamma *, \mathsf{I} >_\gamma \mathsf{C}, \mathsf{D}, \mathsf{E}, \mathsf{F}, \mathsf{H}, \mathsf{K}, \mathsf{N}, \mathsf{Q}, \mathsf{Y} >_\gamma \mathsf{M}, \mathsf{W} \tag{6.13}$$

such that

$$p >_\gamma q \text{ iff } \gamma(p) > \gamma(q) \tag{6.14}$$

where $p, q \in \Phi$ and

$$\gamma(p) = \frac{|V(p)|}{|C|} \tag{6.15}$$

is the fraction of p-codons in the simple model.

6.2.1 Counting codons

Consider first QUANTITY respectively the $\diamondsuit_n^m$-modality. Here the grading within a level of possibility has to be distinguished from the grading across levels of possibility. I start with discussing the former, namely the $>_\diamondsuit^m$-comparator. In the simple model, it holds

that:

$$\text{If } m \geq 3, \text{ then } \gamma_{>^m_\Diamond}(p) = \gamma(p) \text{ for all } p \in \Phi \tag{6.16}$$

where

$$\gamma_{>^m_\Diamond}(p) = \frac{n : \mathfrak{M}, c \Vdash \Diamond !^m_n p}{|\{c' : cR_1 \dots R_m c'\}|} \tag{6.17}$$

is the fraction of p-codons that can be reached via sequences m single substitutions from codon c. That is, the $>^m_\Diamond$-comparator yields the global grading for the third level of possibility or higher. To see this, note the Hamming distance between all codons is maximally three (see section 6.1); so with three subsequent single substitutions, each p-codon can be reached and the count of p-codons equals the size of the block of p-codons in the simple model:

$$\text{If } \mathfrak{M} \Vdash \Diamond !^m_n p \text{ and } m \geq 3, \text{ then } n = |V(p)| \tag{6.18}$$

This gives the following ranking of HbA variants within each level of possibility at codon 6 of *HBB*:

$$\mathfrak{M}, \texttt{GAG} \Vdash \mathsf{D} >^1_\Diamond *, \mathsf{A}, \mathsf{E}, \mathsf{G}, \mathsf{K}, \mathsf{Q}, \mathsf{V} \tag{6.19}$$

$$\mathfrak{M}, \texttt{GAG} \Vdash \mathsf{A}, \mathsf{G}, \mathsf{V} >^2_\Diamond *, \mathsf{D}, \mathsf{E}, \mathsf{K}, \mathsf{Q} >^2_\Diamond \mathsf{M}, \mathsf{P}, \mathsf{S}, \mathsf{T}, \mathsf{W} \tag{6.20}$$

$$\text{If } \mathfrak{M}, \texttt{GAG} \Vdash p >^m_\Diamond q \text{ and } m \geq 3, \text{ then } p >_\gamma q \tag{6.21}$$

See Figure 6.3 for numerical examples.

I now turn to the grading of HbA variants across levels of possibility, namely the $\triangleright^m_\Diamond$-comparator. In the simple model, it holds that:

$$\lim_{m \to \infty} \gamma_{\triangleright^m_\Diamond}(p) = \gamma(p) \text{ for all } p \in \Phi \tag{6.22}$$

where

$$\gamma_{\triangleright^m_\Diamond}(p) = \frac{\sum_{i=1}^{m} n : \mathfrak{M}, c \Vdash \Diamond !^i_n p}{\sum_{i=1}^{m} |\{c' : cR_1 \dots R_i c'\}|} \tag{6.23}$$

is the fraction of p-codons that can be reached via sequences of $1, \dots, m$ single substitu-

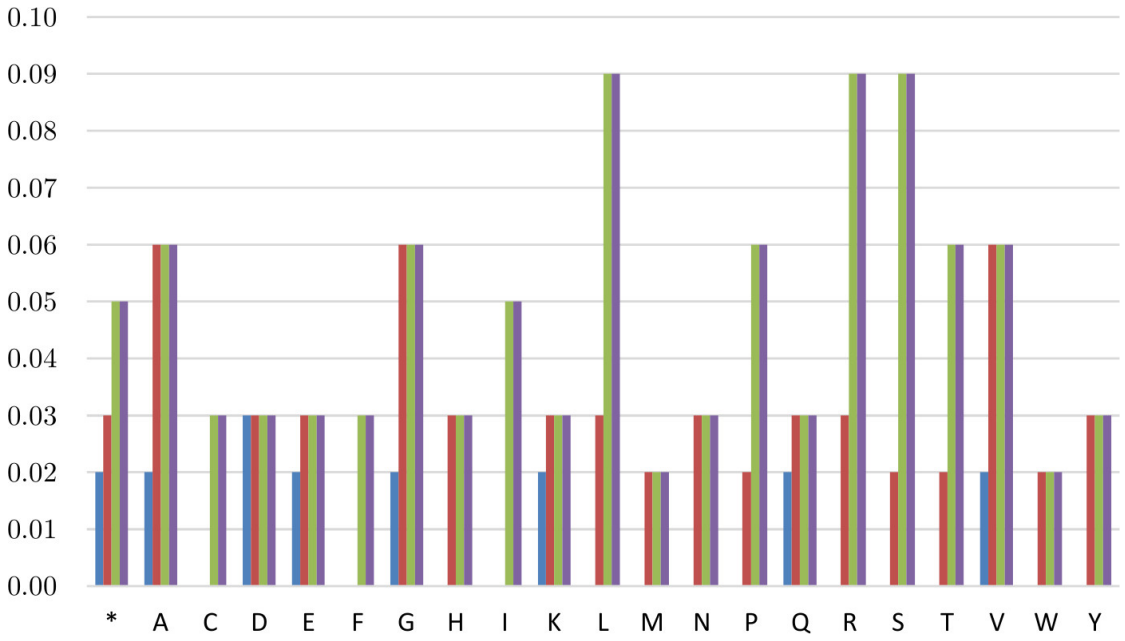


Figure 6.3

Grading of HbA variants within levels of possibility at codon 6 of *HBB* according to QUANTITY in the simple model where $\gamma_{>^1_\Diamond}(p)$ (blue), $\gamma_{>^2_\Diamond}(p)$ (red), $\gamma_{>^3_\Diamond}(p)$ (green), and $\gamma(p)$ (purple) for all $p \in \Phi$ (x-axis).

tions from codon c. That is, the $\rhd^m_\Diamond$-comparator induces a grading that converges to the global grading for high values of m. Depending on how fine-grained a ranking is desired, m can be significantly lowered, however. In what follows, I will assume that rounding to the second decimal place gives a ranking which is sufficiently fine grained. Given this assumption, in the simple model it holds that:

$$\text{If } m \geq 100, \text{ then } \gamma_{\rhd^m_\Diamond}(p) \approx \gamma(p) \text{ for all } p \in \Phi \tag{6.24}$$

That is, the $\rhd^m_\Diamond$-comparator yields the global grading for the hundredth level of possibility or higher. This gives the following grading of HbA variants across levels at codon

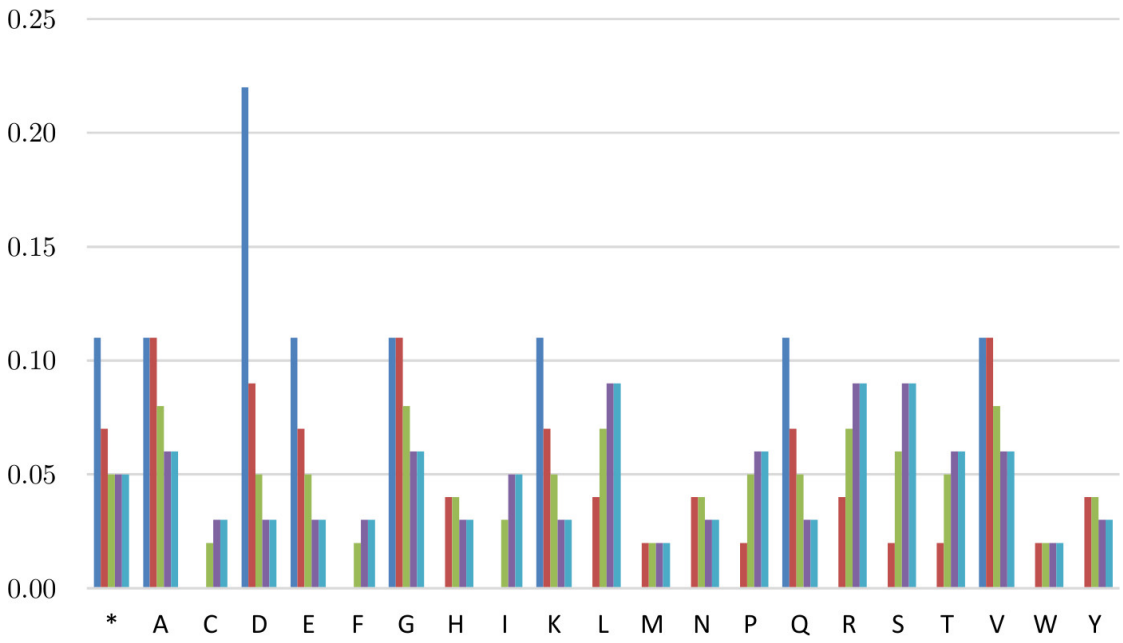


Figure 6.4

Grading of HbA variants across levels of possibility at codon 6 of *HBB* according to QUANTITY in the simple model where $\gamma_{\triangleright^1_\Diamond}(p)$ (blue), $\gamma_{\triangleright^2_\Diamond}(p)$ (red), $\gamma_{\triangleright^3_\Diamond}(p)$ (green), $\gamma_{\triangleright^{100}_\Diamond}(p)$ (purple), and $\gamma(p)$ (turquois) for all $p \in \Phi$ (x-axis).

6 of *HBB*:

$$\mathfrak{M}, \mathtt{GAG} \Vdash \mathsf{D} \triangleright^1_\Diamond *, \mathsf{A}, \mathsf{E}, \mathsf{G}, \mathsf{K}, \mathsf{Q}, \mathsf{V} \tag{6.25}$$

$$\mathfrak{M}, \mathtt{GAG} \Vdash \mathsf{A}, \mathsf{G}, \mathsf{V} \triangleright^2_\Diamond \mathsf{D} \triangleright^2_\Diamond *, \mathsf{E}, \mathsf{K}, \mathsf{Q} \triangleright^2_\Diamond \mathsf{H}, \mathsf{N}, \mathsf{L}, \mathsf{R}, \mathsf{Y} \triangleright^2_\Diamond \mathsf{M}, \mathsf{P}, \mathsf{S}, \mathsf{T}, \mathsf{V} \tag{6.26}$$

$$\mathfrak{M}, \mathtt{GAG} \Vdash \mathsf{A}, \mathsf{G}, \mathsf{V} \triangleright^3_\Diamond \mathsf{L}, \mathsf{R} \triangleright^3_\Diamond \mathsf{S} \triangleright^3_\Diamond *, \mathsf{D}, \mathsf{E}, \mathsf{K}, \mathsf{P}, \mathsf{Q}, \mathsf{T} \triangleright^3_\Diamond \mathsf{H}, \mathsf{N}, \mathsf{Y} \triangleright^3_\Diamond \mathsf{I} \triangleright^3_\Diamond \mathsf{C}, \mathsf{F}, \mathsf{M}, \mathsf{W} \tag{6.27}$$

$$\text{If } \mathfrak{M}, \mathtt{GAG} \Vdash p \triangleright^m_\Diamond q \text{ and } m \geq 100, \text{ then } p >_\gamma q \tag{6.28}$$

See Figure 6.4 for numerical examples and appendix D. for details.

6.2.2 Counting unique sequences of substitutions

Consider now PROCESS respectively the $\diamondsuit_n^m$-modality. Again, the grading within a level of possibility has to be distinguished from the grading across levels of possibility. I start with discussing the former, namely the $>_{\diamondsuit}^m$-comparator. Similar to the $\diamondsuit_n^m$-modality, the $\diamondsuit_n^m$-modality loses the local context of its evaluation codon with higher levels of possibility. More specifically, in the simple model it holds that:

$$\lim_{m\to\infty} \gamma_{>_{\diamondsuit}^m}(p) = \gamma(p) \text{ for all } p \in \Phi \tag{6.29}$$

where

$$\gamma_{>_{\diamondsuit}^m}(p) = \frac{n : \mathfrak{M}, c \Vdash \diamondsuit !_n^m p}{|\{\langle c, \ldots, c' \rangle : cR_1 \ldots R_m c'\}|} = \frac{n : \mathfrak{M}, c \Vdash \diamondsuit !_n^m p}{9^m} \tag{6.30}$$

is the fraction of unique sequences of m single substitutions that reach some p-codon(s) from codon c. For all practical purposes (that is, rounded to two decimal places), it holds that:

$$\text{If } m \geq 8, \text{ then } \gamma_{>_{\diamondsuit}^m}(p) \approx \gamma(p) \text{ for all } p \in \Phi \tag{6.31}$$

That is, the $>_{\diamondsuit}^m$-comparator yields the global grading for the eighth level of possibility or higher. This gives the following grading of HbA variants within each level of possibility at codon 6 of *HBB*:

$$\mathfrak{M}, \texttt{GAG} \Vdash \mathsf{D} >_{\diamondsuit}^1 *, \mathsf{A}, \mathsf{E}, \mathsf{G}, \mathsf{K}, \mathsf{Q}, \mathsf{V} \tag{6.32}$$

$$\mathfrak{M}, \texttt{GAG} \Vdash \mathsf{E} >_{\diamondsuit}^2 \mathsf{A}, \mathsf{G}, \mathsf{V} >_{\diamondsuit}^2 *, \mathsf{D}, \mathsf{H}, \mathsf{K}, \mathsf{L}, \mathsf{N}, \mathsf{Q}, \mathsf{R}, \mathsf{Y} >_{\diamondsuit}^2 \mathsf{M}, \mathsf{P}, \mathsf{S}, \mathsf{T}, \mathsf{W} \tag{6.33}$$

$$\mathfrak{M}, \texttt{GAG} \Vdash \mathsf{A}, \mathsf{G}, \mathsf{V} >_{\diamondsuit}^3 \mathsf{D}, \mathsf{L}, \mathsf{R} >_{\diamondsuit}^3 *, \mathsf{E}, \mathsf{S} >_{\diamondsuit}^3 \mathsf{K}, \mathsf{Q} >_{\diamondsuit}^3 \mathsf{P}, \mathsf{T} >_{\diamondsuit}^3 \mathsf{H}, \mathsf{N}, \mathsf{Y} >_{\diamondsuit}^3 \mathsf{C}, \mathsf{F}, \mathsf{I}, \mathsf{M}, \mathsf{W} \tag{6.34}$$

$$\text{If } \mathfrak{M}, \texttt{GAG} \Vdash p >_{\diamondsuit}^m q \text{ and } m \geq 8, \text{ then } p >_\gamma q \tag{6.35}$$

See Figure 6.5 for numerical examples.

I now turn to the grading of HbA variants across levels of possibility, namely the $\rhd_{\diamondsuit}^m$-comparator. In the simple model it holds that:

$$\lim_{m\to\infty} \gamma_{\rhd_{\diamondsuit}^m}(p) = \gamma(p) \text{ for all } p \in \Phi \tag{6.36}$$

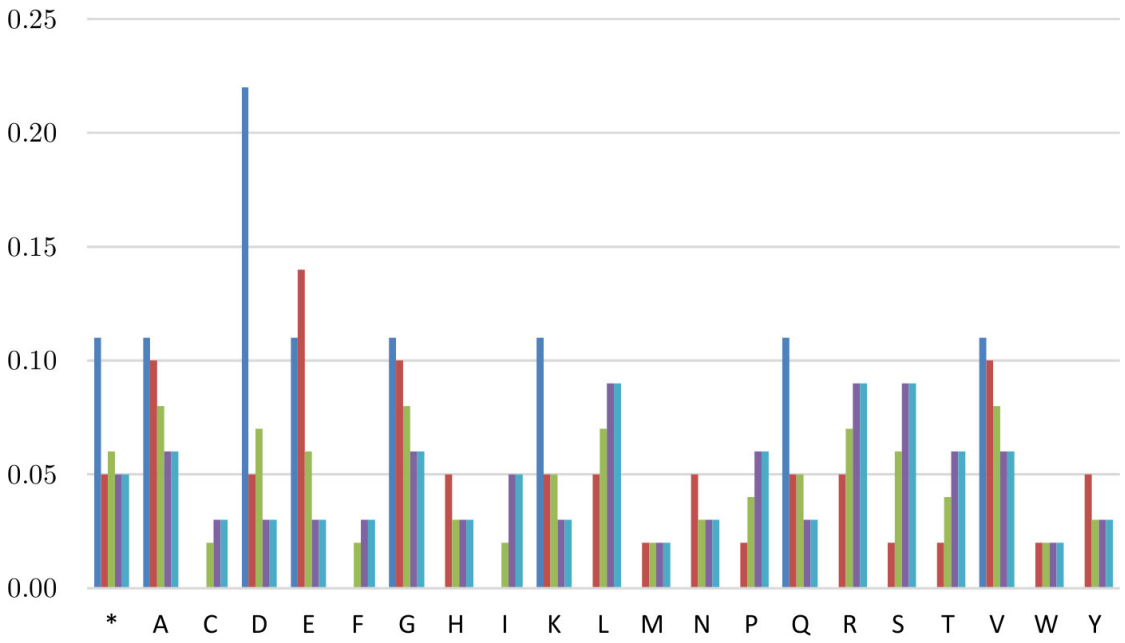


Figure 6.5

Grading of HbA variants within levels of possibility at codon 6 of *HBB* according to PROCESS in the simple model where $\gamma_{>\overset{1}{\diamond}}(p)$ (blue), $\gamma_{>\overset{2}{\diamond}}(p)$ (red), $\gamma_{>\overset{3}{\diamond}}(p)$ (green), $\gamma_{>\overset{8}{\diamond}}(p)$ (purple), and $\gamma(p)$ (turquois) for all $p \in \Phi$ (x-axis).

where

$$\gamma_{\triangleright\overset{m}{\diamond}}(p) = \frac{\sum_{i=1}^{m} n : \mathfrak{M}, c \Vdash \diamond !_n^i p}{\sum_{i=1}^{m} |\{\langle c, \ldots, c' \rangle : cR_1 \ldots R_i c\}|} = \frac{\sum_{i=1}^{m} n : \mathfrak{M}, c \Vdash \diamond !_n^i p}{\sum_{i=1}^{m} 9^i} \tag{6.37}$$

is the fraction of unique sequences of $1, \ldots, m$ single substitutions that reach some p-codon(s) from codon c. Again, for all practical purposes (that is, rounded to two decimal places), it holds that:

$$\text{If } m \geq 8, \text{ then } \gamma_{\triangleright\overset{m}{\diamond}}(p) \approx \gamma(p) \text{ for all } p \in \Phi \tag{6.38}$$

That is, the $\triangleright\overset{m}{\diamond}$-comparator yields the global grading for the eight level of possibility or higher. This gives the following grading of HbA variants across levels at codon 6 of

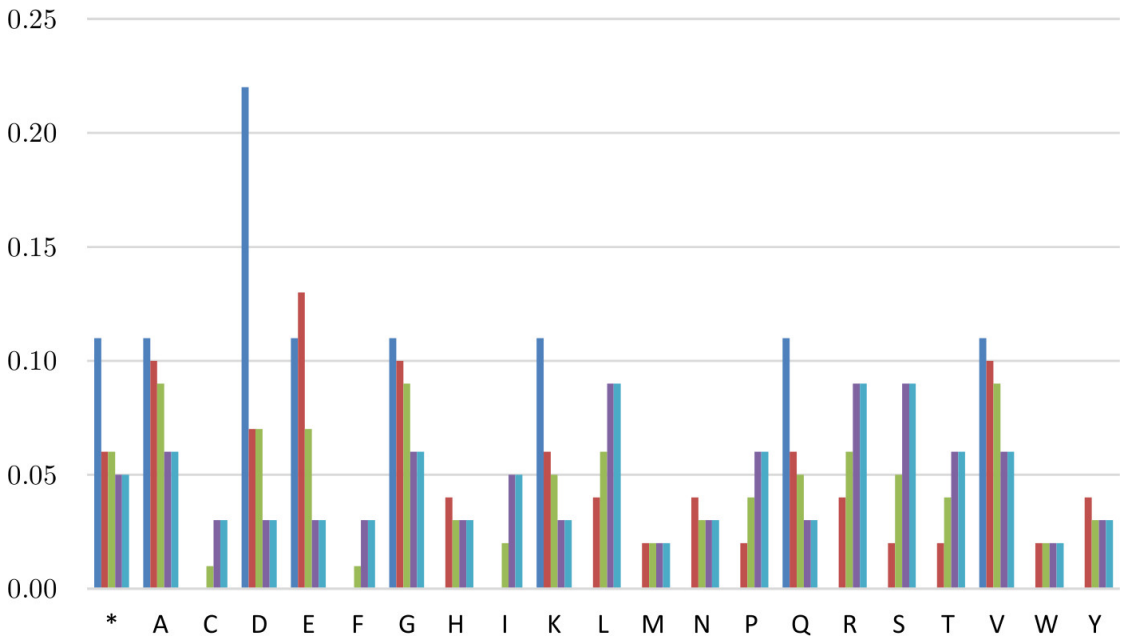


Figure 6.6

Grading of HbA variants across levels of possibility at codon 6 of *HBB* according to PROCESS in the simple model where $\gamma_{\rhd^1_\diamond}(p)$ (blue), $\gamma_{\rhd^2_\diamond}(p)$ (red), $\gamma_{\rhd^3_\diamond}(p)$ (green), $\gamma_{\rhd^8_\diamond}(p)$ (purple), and $\gamma(p)$ (turquois) for all $p \in \Phi$ (x-axis).

HBB:

$$\mathfrak{M}, \mathtt{GAG} \Vdash \mathsf{D} \rhd^1_\diamond *, \mathsf{A}, \mathsf{E}, \mathsf{G}, \mathsf{K}, \mathsf{Q}, \mathsf{V} \tag{6.39}$$

$$\mathfrak{M}, \mathtt{GAG} \Vdash \mathsf{E} \rhd^2_\diamond \mathsf{A}, \mathsf{G}, \mathsf{V} \rhd^2_\diamond \mathsf{D} \rhd^2_\diamond *, \mathsf{K}, \mathsf{Q} \rhd^2_\diamond \mathsf{H}, \mathsf{L}, \mathsf{N}, \mathsf{R}, \mathsf{Y} \rhd^2_\diamond \mathsf{M}, \mathsf{P}, \mathsf{S}, \mathsf{T}, \mathsf{W} \tag{6.40}$$

$$\mathfrak{M}, \mathtt{GAG} \Vdash \mathsf{A}, \mathsf{G}, \mathsf{V} \rhd^3_\diamond \mathsf{D}, \mathsf{E} \rhd^3_\diamond *, \mathsf{L}, \mathsf{R} \rhd^3_\diamond \mathsf{K}, \mathsf{Q}, \mathsf{S} \rhd^3_\diamond \mathsf{P}, \mathsf{T} \rhd^3_\diamond \mathsf{H}, \mathsf{N}, \mathsf{Y} \rhd^3_\diamond \mathsf{I}, \mathsf{M}, \mathsf{W} \rhd^3_\diamond \mathsf{C}, \mathsf{F} \tag{6.41}$$

$$\text{If } \mathfrak{M}, \mathtt{GAG} \Vdash p \rhd^m_\diamond q \text{ and } m \geq 8, \text{ then } p >_\gamma q \tag{6.42}$$

See Figure 6.6 for numerical examples and appendix D. for details.

6.3 Probability

There are a number of probabilistic modal logics which are mostly used in formal epistemology in order to model various notions of knowledge and belief. Here I will propose an implementation of PROBABILITY based on the probabilistic modal logic of Shirazi and Amir (2007, 2008) which models probabilistic knowledge.[1]

6.3.1 Probabilistic model

In this section, I work within the framework of Shirazi and Amir (2007, 2008) which in turn is based on Fagin and Halpern (1994). For this, I adapt their logic to a non-epistemic context and extend it via a number of modalities and comparative operators. By this I mean that the probabilistic model and the probabilistic amino acid language are not defined in terms of knowledge and believe of an actor; I do not mean that the discussed probability distributions are non-epistemic or non-heuristic. I start by defining a probabilistic model:

Definition 6.2 (Probabilistic model)
A probabilistic model $\mathfrak{M}^{\mathfrak{P}}$ is a quadruple $\left\langle C^{\mathfrak{P}}, P^{\mathfrak{P}}, \Phi^{\mathfrak{P}}, V^{\mathfrak{P}} \right\rangle$ such that:

- $C^{\mathfrak{P}}$ is the set of codons C as per definition 5.1.
- $P^{\mathfrak{P}} : C^{\mathfrak{P}} \times C^{\mathfrak{P}} \to \mathbb{R}$ is a conditional probability function interpreted as single substitution. The probability that $c' \in C^{\mathfrak{P}}$ can be reached from $c \in C^{\mathfrak{P}}$ via single substitution is written as $P^{\mathfrak{P}}(c'|c)$ and constrained by:

$$0 \leq P^{\mathfrak{P}}(c'|c) \leq 1 \tag{6.43}$$

$$\sum_{c' \in C^{\mathfrak{P}}} P^{\mathfrak{P}}(c'|c) = 1 \tag{6.44}$$

- $\Phi^{\mathfrak{P}}$ is the set of atomic propositions Φ as per definition 5.1.
- $V^{\mathfrak{P}} : \Phi^{\mathfrak{P}} \to \mathcal{P}(C^{\mathfrak{P}})$ is the valuation V as per definition 5.1.

I now turn to the definition of the probabilistic amino acid language:

[1] Another suitable starting point are discrete conditional probabilistic models for knowledge and conditional belief due to Baltag and Smets (2006a,b, 2007).

Definition 6.3 (Probabilistic amino acid language)
The probabilistic amino acid language $\mathcal{L}^{\mathcal{P}}$ is used to describe probabilistic models $\mathfrak{M}^{\mathfrak{P}} = \left\langle C^{\mathfrak{P}}, P^{\mathfrak{P}}, \Phi^{\mathfrak{P}}, V^{\mathfrak{P}} \right\rangle$. The syntax of $\mathcal{L}^{\mathcal{P}}$ is given by the following Backus-Naur form:

$$\phi \;:=\; p \mid \neg\phi \mid \phi \vee \phi \mid \;\circledast\, \phi = \alpha$$

where $p \in \Phi^{\mathfrak{P}}$ and $\alpha \in \mathbb{R}$. The standard abbreviations for the classical connectives $\wedge, \rightarrow, \leftrightarrow$ are used; in addition, it is convenient to use:

$$\phi >_{\circledast} \psi := \circledast\phi = \alpha \wedge \circledast\psi = \beta \text{ and } \alpha > \beta \tag{6.45}$$

where $\alpha, \beta \in \mathbb{R}$. The semantics of $\mathcal{L}^{\mathcal{P}}$ are identical to $\mathcal{L}$ as per definition 5.2 for non-modal formulas. The semantics for the modal operator are:

$$\mathfrak{M}^{\mathfrak{P}}, c \Vdash \circledast\phi = \alpha \text{ iff } \sum_{c' \in S} P^{\mathfrak{P}}(c'|c) = \alpha \tag{6.46}$$

where $S = \{c' \in C^{\mathfrak{P}} : \mathfrak{M}^{\mathfrak{P}}, c' \Vdash \phi\}$.

$\circledast\phi = \alpha$ expresses that a ϕ-codon can be reached via a single substitution with a probability of α. The literal meaning of $\phi >_{\circledast} \psi$ is that the probability of reaching of ϕ-codon via single substitution is higher than the probability of reaching a ψ-codon via single substitution; the intended meaning, in line with Probability, is that ϕ is more possible than ψ.

In the following, the grading of HbA variants caused by single substitutions at codon 6 of *HBB* will be discussed in the context of Probability. What distinguishes Probability from Simplicity, Quantity and Process is that with the choice of the probability function, additional empirical content can be added to the model. I will focus on three distinct probability functions and corresponding models: First, a constant probability function; the intention here is to underscore some features and limitations of the probabilistic amino acid language. Second, I will show how empirical content can be added at the DNA level by providing a probability function which captures the so-called transition/transversion bias. And finally, I do the same for the protein level by constructing a probability function based on amino acid scoring matrices.

6.3.2 Constant probability function

Let $\mathfrak{M}^{\mathfrak{C}} = \left\langle C^{\mathfrak{C}}, P^{\mathfrak{C}}, \Phi^{\mathfrak{C}}, V^{\mathfrak{C}} \right\rangle$ be a probabilistic model with a constant probability function $P^{\mathfrak{C}}$ such that:

$$P^{\mathfrak{C}}(c'|c) = \begin{cases} \frac{1}{9} & \text{if } cRc' \\ 0 & \text{otherwise} \end{cases} \tag{6.47}$$

where R is the substitution relation of the simple model. That is, from each codon, nine codons can be reached via single substitution, and reaching each such codon gets assigned the same probability. This gives the following ranking of HbA within the first level of possibility at codon 6 of *HBB* (missing amino acids are not possible since they have a zero probability of being reached via single substitution):

$$\mathfrak{M}^{\mathfrak{C}}, \mathtt{GAG} \vDash \mathsf{D} >_{\circledast} *, \mathsf{A}, \mathsf{E}, \mathsf{G}, \mathsf{K}, \mathsf{Q}, \mathsf{V} \tag{6.48}$$

For example, aspartate D is more possible than termination $*$ at codon 6 since:

$$\sum_{c \in S} P^{\mathfrak{C}}(c|\mathtt{GAG}) = P^{\mathfrak{C}}(\mathtt{GAC}|\mathtt{GAG}) + P^{\mathfrak{C}}(\mathtt{GAT}|\mathtt{GAG}) = \frac{1}{9} + \frac{1}{9} = \frac{2}{9} \tag{6.49}$$

$$\sum_{c \in S'} P^{\mathfrak{C}}(c|\mathtt{GAG}) = P^{\mathfrak{C}}(\mathtt{TAA}|\mathtt{GAG}) + P^{\mathfrak{C}}(\mathtt{TAG}|\mathtt{GAG}) + P^{\mathfrak{C}}(\mathtt{TGA}|\mathtt{GAG}) = 0 + \frac{1}{9} + 0 = \frac{1}{9} \tag{6.50}$$

where $S = \{c \in C^{\mathfrak{C}} : \mathfrak{M}^{\mathfrak{C}}, c \Vdash \mathsf{D}\}$ and $S' = \{c \in C^{\mathfrak{C}} : \mathfrak{M}^{\mathfrak{C}}, c \Vdash *\}$; and similar for $\mathsf{A}, \mathsf{E}, \mathsf{G}, \mathsf{K}, \mathsf{Q}$ and V.

Now, what about the grading within higher levels of possibility and the grading across levels of possibility? Unfortunately, neither can be expressed in the probabilistic amino acid language. To see this, consider a nested formula such as $\circledast(\circledast\phi = \alpha) = \beta$. It expresses that with a probability of β a codon can be reached via single substitution at which there is a probability of α that a ϕ-codon can be reached via single substitution. However, the probability that a ϕ-codon can be reached via two subsequent single substitutions cannot be computed on the basis of α and β; see Figure 6.7 for an example. In order to achieve a grading within higher levels of possibility and across levels of possibility, the probabilistic amino acid language has to be extended:

Definition 6.4 (Extended probabilistic amino acid language)
The extended probabilistic amino acid language $\mathcal{L}^{\mathcal{E}}$ is used to describe probabilistic models $\left\langle C^{\mathfrak{P}}, P^{\mathfrak{P}}, \Phi^{\mathfrak{P}}, V^{\mathfrak{P}} \right\rangle$. The syntax of $\mathcal{L}^{\mathcal{E}}$ is given by the following Backus-Naur form:

$$\phi \;:=\; p \mid \neg\phi \mid \phi \vee \phi \mid \;\circledast^{m} \phi = \alpha$$

where $p \in \Phi^{\mathfrak{P}}$, $m \in \mathbb{N}$ and $\alpha \in \mathbb{R}$. The standard abbreviations for the classical connectives $\wedge, \rightarrow, \leftrightarrow$ are used; in addition, it is convenient to use:

$$\phi >^{m}_{\circledast} \psi := \circledast^{m}\phi = \alpha \wedge \circledast^{m}\psi = \beta \text{ and } \alpha > \beta \tag{6.51}$$

$$\phi \rhd^{m}_{\circledast} \psi := \bigwedge_{i=1}^{m} \circledast^{i}\phi = \alpha_i \wedge \bigwedge_{i=1}^{m} \circledast^{i}\phi = \beta_i \text{ and } \sum_{i=1}^{m}\alpha_i > \sum_{i=1}^{m}\beta_i \tag{6.52}$$

where $\alpha, \beta \in \mathbb{R}$. The semantics of $\mathcal{L}^{\mathcal{E}}$ are identical to $\mathcal{L}$ as per definition 5.2 for non-modal formulas. The semantics for the modal operator are:

$$\mathfrak{M}^{\mathfrak{P}}, c \Vdash \circledast^{m}\phi = \alpha \text{ iff } \sum_{t \in (C^{\mathfrak{P}})^{m}} g(t) = \alpha \tag{6.53}$$

where $(C^{\mathfrak{P}})^{m} = \underbrace{C^{\mathfrak{P}} \times \cdots \times C^{\mathfrak{P}}}_{m}$ such that $t \in (C^{\mathfrak{P}})^{m}$ is an m-tuple $\langle c_1, \ldots, c_m \rangle$ and $g : (C^{\mathfrak{P}})^{m} \rightarrow \mathbb{R}$ is a function such that:

$$g(\langle c_1, \ldots, c_m \rangle) = \begin{cases} \prod_{i=1}^{m-1} P^{\mathfrak{P}}(c_{i+1}|c_i) & \text{if } \mathfrak{M}^{\mathfrak{P}}, c_m \Vdash \phi \text{ and } c_1 = c \\ 0 & \text{otherwise} \end{cases} \tag{6.54}$$

$\circledast^{m}\phi = \alpha$ expresses that the probability of reaching a ϕ-codon via a sequence of m single substitutions is α. The $\circledast^{m}$-can be thought of as the probabilistic variant of the $\Diamond$- and $\diamond$-modality of the counting amino acid language (see definition 6.1). Note that the $\circledast^{1}$-modality is equivalent to the $\circledast$-modality of the probabilistic amino acid language. At the heart of the extension, however, are the two comparators $>^{m}_{\circledast}$ and $\rhd^{m}_{\circledast}$. The literal meaning of $\phi >^{m}_{\circledast} \psi$ is that the probability of reaching a ϕ-codon via a sequence of m single substitutions is higher than the probability of reaching a ψ-codon via a sequence of m single substitutions; the intended meaning is that ϕ is more possible than ψ within a level of possibility m. The literal meaning of $\phi \rhd^{m}_{\circledast} \psi$ is that the probability of reaching a ϕ-codon via a sequence of up to m single substitutions is higher than the probability of

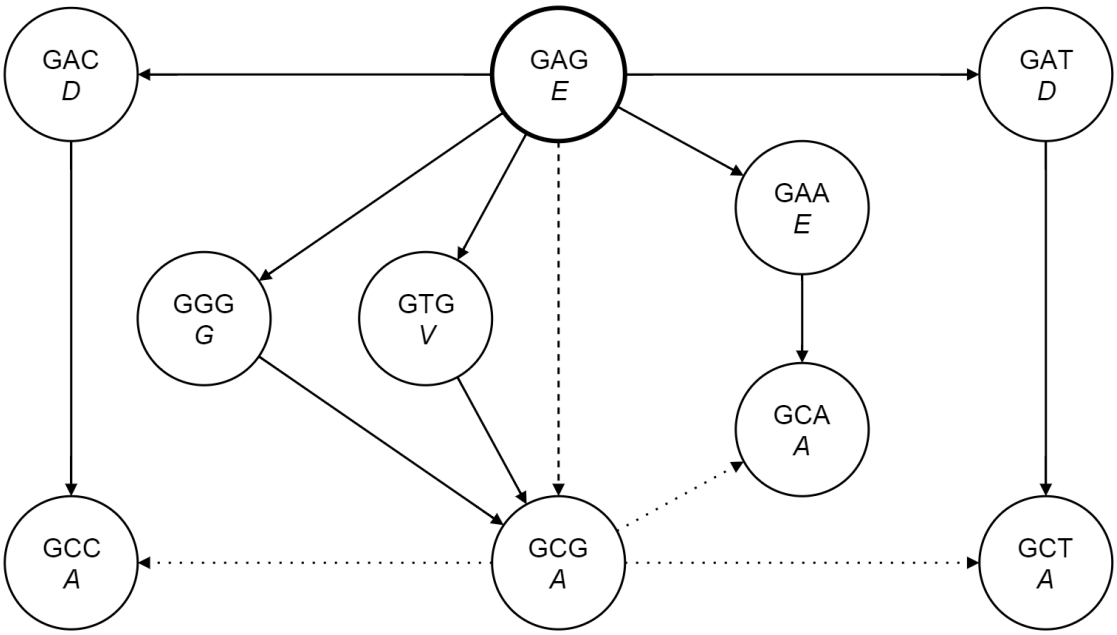


Figure 6.7

This partial representation of the probabilistic model $\mathfrak{M}^{\mathfrak{C}}$ as directed graph shows all possible sequences of two single substitions to reach an A-codon from codon 6 of *HBB* (bold circle). For any pair of nodes $\langle n, n' \rangle$, an arrow from n to n' represents $P^{\mathfrak{C}}(n'|n) = \frac{1}{9}$. The probability that an A-codon can be reached from codon 6 via two subsequent single substitutions is $8 \times \frac{1}{9} \times \frac{1}{9} = \frac{8}{81}$ since there are eight double-arrows (i.e., composed arrows) reaching an A-codon from codon 6. In $\mathcal{L}^{\mathcal{P}}$, this cannot be expressed. However, we can express that $\otimes(\otimes \mathsf{A} = \frac{1}{3}) = \frac{1}{9}$ which tells us that the probabilistic model is such that there is exactly one codon that can be reached via single substitution (dashed arrow) from which exactly three A-codons can be reached via single substitution (dotted arrows). By contrast, in $\mathcal{L}^{\mathcal{E}}$ we can express that $\otimes^2 \mathsf{A} = \frac{8}{81}$, as wanted.

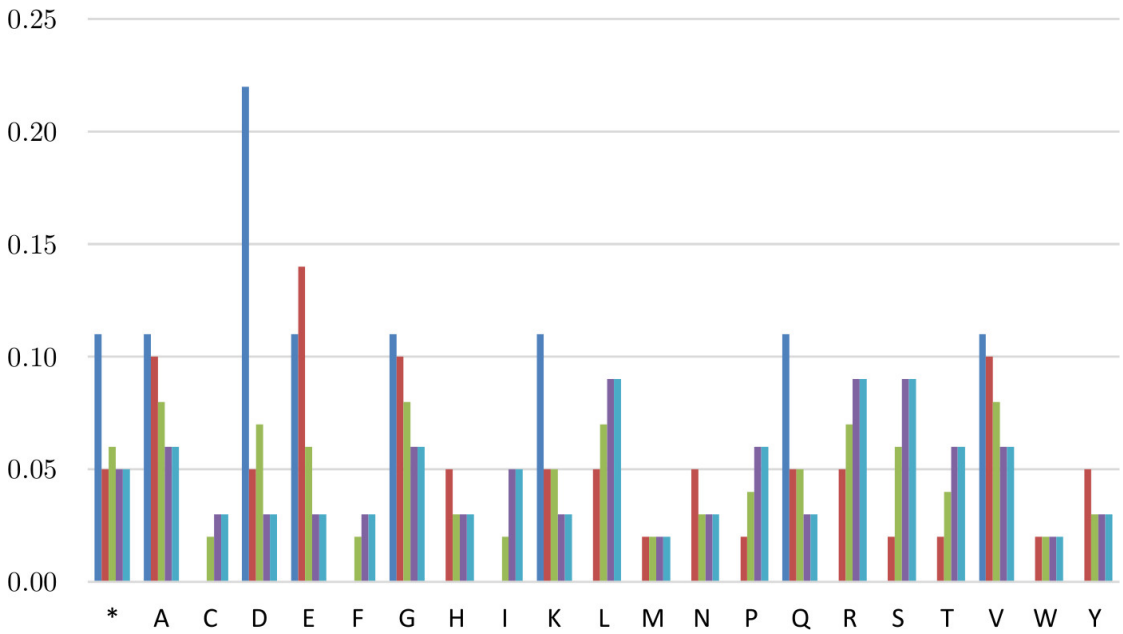


Figure 6.8

Grading of HbA variants within levels of possibility at codon 6 of *HBB* according to PROBABILITY in the probabilistic model $\mathfrak{M}^{\mathfrak{C}}$ where $\circledast^1 p = \alpha$ (blue), $\circledast^2 p = \alpha$ (red), $\circledast^3 p = \alpha$ (green), $\circledast^8 p = \alpha$ (purple), and $\gamma(p) = \alpha$ (turquois) for all $p \in \Phi$ (x-axis).

reaching a ψ-codon via a sequence of up to m single substitutions; the intended meaning is that ϕ is more possible than ψ across the levels possibility $1, \ldots, m$.

So with $\mathcal{L}^{\mathcal{E}}$ in place, consider the grading of HbA within higher levels and possibility and across levels of possibility. I start with the former. In the probabilistic model $\mathfrak{M}^{\mathfrak{C}}$, it holds that:

$$\lim_{m \to \infty} \circledast^m p = \gamma(p) \text{ for all } p \in \Phi^{\mathfrak{C}} \tag{6.55}$$

That is, for high values of m, the probability that a p-codon can be reached via a sequence of m single substitutions is the probability of drawing a p-codon from the set of codons $\mathfrak{C}^{\mathfrak{C}}$. Note that in contrast to section 6.2, $\gamma(p)$ as stated in (6.15) is interpreted probabilistically. For all practical purposes (that is, rounded to two decimal places), it holds that:

$$\text{If } m \geq 8, \text{ then } \circledast^m p \approx \gamma(p) \text{ for all } p \in \Phi^{\mathfrak{C}} \tag{6.56}$$

This can be expressed by employing the $>^m_{\otimes}$-comparator and yields the following grading of HbA variants within each level of possibility at codon 6 of *HBB*:

$$\mathfrak{M}^{\mathfrak{C}}, \mathtt{GAG} \Vdash \mathsf{D} >^1_{\otimes} *, \mathsf{A}, \mathsf{E}, \mathsf{G}, \mathsf{K}, \mathsf{Q}, \mathsf{V} \quad (6.57)$$

$$\mathfrak{M}^{\mathfrak{C}}, \mathtt{GAG} \Vdash \mathsf{E} >^2_{\otimes} \mathsf{A}, \mathsf{G}, \mathsf{V} >^2_{\otimes} *, \mathsf{D}, \mathsf{H}, \mathsf{K}, \mathsf{L}, \mathsf{N}, \mathsf{Q}, \mathsf{R}, \mathsf{Y} >^2_{\otimes} \mathsf{M}, \mathsf{P}, \mathsf{S}, \mathsf{T}, \mathsf{W} \quad (6.58)$$

$$\mathfrak{M}, \mathtt{GAG} \Vdash \mathsf{A}, \mathsf{G}, \mathsf{V} >^3_{\otimes} \mathsf{D}, \mathsf{L}, \mathsf{R} >^3_{\otimes} *, \mathsf{E}, \mathsf{S} >^3_{\otimes} \mathsf{K}, \mathsf{Q} >^3_{\otimes} \mathsf{P}, \mathsf{T} >^3_{\otimes} \mathsf{H}, \mathsf{N}, \mathsf{Y} >^3_{\otimes} \mathsf{C}, \mathsf{F}, \mathsf{I}, \mathsf{M}, \mathsf{W} \quad (6.59)$$

$$\text{If } \mathfrak{M}^{\mathfrak{C}}, \mathtt{GAG} \Vdash p >^m_{\otimes} q \text{ and } m \geq 8, \text{ then } p >_{\gamma} q \quad (6.60)$$

See Figure 6.8 for numerical examples and appendix D. for details. Note that by construction of the model at hand, this grading is identical to the grading within levels of possibility in the simple model provided above in section 6.2 by PROCESS respectively the $\diamond^m_n$-modality. More precisely, given the semantics of the $\otimes^m$-modality as stated in definitions (6.53) and (6.54), the probability α in $\otimes^m p = \alpha$ is computed by taking the sum of the probabilities of each unique sequence of m single substitutions that reaches a p-codon. But since each such sequence has equal weight thanks to the underlying constant probability function, α is simply the number of sequences (relative to the total number of unique sequences). And this is what is captured by the $\diamond^m_n$-modality as per definition (6.12).

This completes the discussion of the probabilistic model with a uniform probability distribution.

6.3.3 Transition/transversion bias based probability function

Let me now turn to probabilistic models with more interesting probability functions. On the DNA level, substitutions are classified either as transitions or as transversions (see Figure 4.3). Given that there are twice as many possible transversions ($\mathtt{A} \rightharpoonup \mathtt{C}, \mathtt{C} \rightharpoonup \mathtt{G}, \mathtt{G} \rightharpoonup \mathtt{T}, \mathtt{T} \rightharpoonup \mathtt{A}$ and vice versa) as there are possible transitions ($\mathtt{A} \rightharpoonup \mathtt{G}, \mathtt{C} \rightharpoonup \mathtt{T}$ and vice versa), the expected ratio of transitions to transversions is:

$$\kappa_{\text{expected}} = \frac{\text{number of possible transitions } n}{\text{number of possible transversions}} = \frac{n}{2 \times n} = \frac{4}{2 \times 4} = 0.5 \quad (6.61)$$

However, κ_{observed} is significantly higher than κ_{expected} for most genes and species where:

$$\kappa_{\text{observed}} = \frac{\text{number of observed transitions}}{\text{number of observed transversions}} \quad (6.62)$$

	HS	HS*	DM	EC*
A ⇝ G and T ⇝ C	0.13	0.17	0.18	0.12
G ⇝ A and C ⇝ T	0.38	0.37	0.30	0.44
A ⇝ C and T ⇝ G	0.12	0.09	0.10	0.14
A ⇝ T and T ⇝ A	0.14	0.14	0.09	0.13
G ⇝ C and C ⇝ G	0.14	0.10	0.13	0.06
G ⇝ T and C ⇝ A	0.09	0.13	0.20	0.11
κ_{expected}	0.5	0.5	0.5	0.5
κ_{observed}	1.04	1.17	0.92	1.27
κ_{bias}	2.08	2.34	1.84	2.54

Table 6.1

Transition/transversion bias in *Homo sapiens* (HS), *Drosophila melanogaster*(DM) and *Escherichia coli* (EC) based on Lynch (2007: 125). The top rows indicate transitions; the middle rows indicate transversions; the bottom rows indicate the expected and observed ratios of transitions to transversions as well as the corresponding transition/transition bias. The data is based on direct observations of reporter constructs respectively phylogenetic analyses of pseudogenes if marked with an asterix.

The factor of the mismatch between κ_{observed} and κ_{expected} is the so-called transition/ transversion bias:

$$\kappa_{\text{bias}} = \frac{\kappa_{\text{observed}}}{\kappa_{\text{expected}}} \tag{6.63}$$

It is generally assumed that $\kappa_{\text{bias}} \approx 2$ for most genes and species (but see Keller et al. 2007 for the inevitable counter-example) even though the exact cause of transition/ transversion bias is still an open question (see Stoltzfus and Norris 2015); see Table 6.1 for some examples.

In the following, I will construct a probabilistic model $\mathfrak{M}^{\mathfrak{B}} = \left\langle C^{\mathfrak{B}}, P^{\mathfrak{B}}, \Phi^{\mathfrak{B}}, V^{\mathfrak{B}} \right\rangle$ that takes into account transition/transversion bias. This enables a transition/transversion bias sensitive grading of HbA variants caused by single substitutions at codon 6 of *HBB*. Put differently, by building transition/transversion bias into the model, the abstraction of not distinguishing between transitions and transversions is removed. This is achieved in two steps:

First, fix the transition/transversion bias. For lack of data specific to *HBB*, we assume

that:

$$\kappa_{\text{bias}}(HBB) = \kappa_{\text{bias}}(\text{human}) \tag{6.64}$$

The genome wide transition/transversion bias for humans $\kappa_{\text{bias}}(\text{human})$ is 2.08 or 2.34 depending on whether $\kappa_{\text{observed}}(\text{human})$ is derived from direct observations of reporter constructs or phylogenetic analyses of pseudogenes (Lynch 2007: 125). As per Table 6.1, we have:

$$\kappa_{\text{bias}}(HBB) = \frac{\kappa_{\text{observed}}(HBB)}{\kappa_{\text{expected}}(HBB)} = \frac{1.04}{0.5} = 2.08 \tag{6.65}$$

Second, define the probability function $P^{\mathfrak{B}}$. Here, in addition to the constraints (6.43) and (6.44) imposed by definition 6.2, in order to accommodate (6.65), it must hold that:

$$\frac{\sum\limits_{c' \in S} P^{\mathfrak{B}}(c'|c)}{\sum\limits_{c' \in S'} P^{\mathfrak{B}}(c'|c)} = 1.04 \tag{6.66}$$

where $S = \{c' \in C^{\mathfrak{B}} : c \rightsquigarrow c' \text{ is a transition}\}$ and $S' = \{c' \in C^{\mathfrak{B}} : c \rightsquigarrow c' \text{ is a transversion}\}$. For construction, take again R, namely the substitution relation of the simple model. Then the probability function $P^{\mathfrak{B}}$ is given by:

$$P^{\mathfrak{B}}(c'|c) = \begin{cases} \frac{0.51}{3} & \text{if } cRc' \text{ and } c \rightsquigarrow c' \text{ is a transition} \\ \frac{0.49}{6} & \text{if } cRc' \text{ and } c \rightsquigarrow c' \text{ is a transversion} \\ 0 & \text{otherwise} \end{cases} \tag{6.67}$$

So we increase the probability of transitions over transversions in the model in order to account for the transition/transversion bias. Note that this assumes a uniform probability distribution within both the block of transitions and the block of transversions for ease of presentation (a more detailed treatment requires transparent modalities, see subsection 7.2.2). This yields the following grading of HbA within levels of possibility

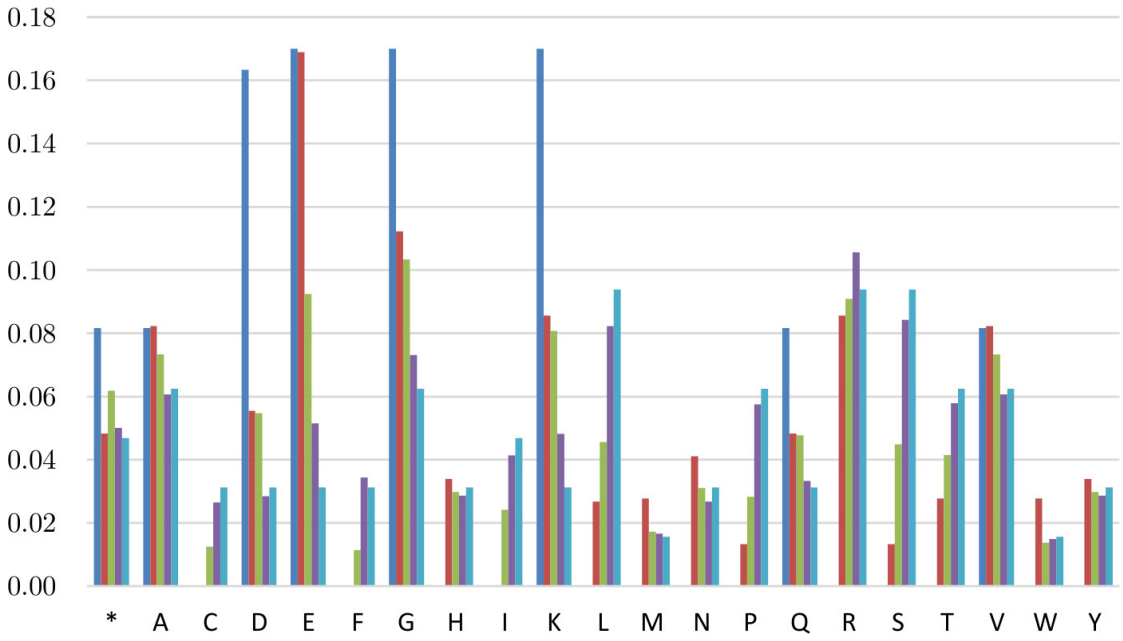


Figure 6.9

Grading of HbA variants within levels of possibility at codon 6 of *HBB* according to PROBABILITY in the probabilistic model $\mathfrak{M}^{\mathfrak{B}}$ where $\otimes^1 p = \alpha$ (blue), $\otimes^2 p = \alpha$ (red), $\otimes^3 p = \alpha$ (green), $\otimes^7 p = \alpha$ (purple), and $\gamma(p) = \alpha$ (turquois) for all $p \in \Phi$ (x-axis).

at codon 6 of *HBB*:

$$\mathfrak{M}^{\mathfrak{B}}, \mathtt{GAG} \vDash \mathsf{E}, \mathsf{G}, \mathsf{K} >^1_{\otimes} \mathsf{D} >^1_{\otimes} *, \mathsf{A}, \mathsf{Q}, \mathsf{V} \tag{6.68}$$

$$\mathfrak{M}^{\mathfrak{B}}, \mathtt{GAG} \vDash \mathsf{E} >^2_{\otimes} \mathsf{G} >^2_{\otimes} \mathsf{K}, \mathsf{R} >^2_{\otimes} \mathsf{A}, \mathsf{V} >^2_{\otimes} \mathsf{D} >^2_{\otimes} *, \mathsf{Q} >^2_{\otimes} \mathsf{N} >^2_{\otimes} \mathsf{H}, \mathsf{L}, \mathsf{M}, \mathsf{T}, \mathsf{W}, \mathsf{Y} >^2_{\otimes} \mathsf{P}, \mathsf{S} \tag{6.69}$$

$$\mathfrak{M}^{\mathfrak{B}}, \mathtt{GAG} \vDash \mathsf{R} >^7_{\otimes} \mathsf{L}, \mathsf{S} >^7_{\otimes} \mathsf{G} >^7_{\otimes} \mathsf{A}, \mathsf{P}, \mathsf{T}, \mathsf{V} >^7_{\otimes} *, \mathsf{E}, \mathsf{K} >^7_{\otimes} \mathsf{I} >^7_{\otimes} \mathsf{C}, \mathsf{D}, \mathsf{F}, \mathsf{N}, \mathsf{H}, \mathsf{Q}, \mathsf{Y} >^7_{\otimes} \mathsf{M} >^7_{\otimes} \mathsf{W} \tag{6.70}$$

See Figure 6.9 for numerical examples and appendix D. for details. Here it is important to note that in contrast to the examples of gradings within levels of possibility discussed above, a prediction for whether and when the global grading is reached is not provided. The reason is that the employed algorithm does not scale well for large inputs; this is related to issues discussed in more detail in section 8.3.

6.3.4 Amino acid scoring matrix based probability function

Instead of defining the probability function of a probabilistic model based on observations at the DNA level as in the previous subsection, the probability function can also be defined based on observations at the protein level. In this subsection, I will show how tools and results from bioinformatics can be employed to achieve this purpose. More specifically, I will construct a probabilistic model where the probability function is built from the PAM amino acid scoring matrix. Note that from a modeling perspective this is unusual: The frame (that is, the probability function) is defined at least partially in terms of the valuation.

I start by briefly introducing amino acid scoring matrices. In sequence alignment algorithms, scoring matrices are used in order quantify the probability of substitutions (Xiong 2006: 41). Let a be a variable ranging over the amino acids. An amino acid scoring matrix is a 20×20 real matrix $\mathbf{M}$ with the amino acids as rows and columns where each element $\mathbf{m}_{\mathsf{a},\mathsf{a}'}$ is as score interpreted as the probability of substituting an amino acid a' with an amino acid a. Such matrices come in two flavors, analytic and empirical. In analytic matrices, the scores are derived from the chemical properties of the amino acids. By contrast, in empirical matrices, the scores are based on observations of the actual alignments of (highly) similar sequences; in general, empirical matrices are better predictors than analytic matrices (Xiong 2006: 42). Two of the most popular amino acid scoring matrices are PAM (Point Accepted Mutation matrix, Dayhoff et al. 1978) and BLOSUM (Block Subsitution Matrix, Henikoff and Henikoff 1992).

I will now consider PAM in more detail. Note that for this section, not the actual scores but rather the probability distribution from which these scores are derived is important. This is why I will focus on PAM mutation probability matrices and neglect the more common PAM log-odds scoring matrices in what follows.

Consider first some terminology. A PAM unit $n \in \mathbb{N}$ is a measure of evolutionary distance and defined as n accepted point mutations per 100 amino acids. The crucial notion here is of course that of an accepted point mutation:

> An accepted point mutation in a protein is a replacement of one amino acid by another, accepted by natural selection. It is the result of two distinct processes: the first is the occurrence of a mutation in the portion of the gene template producing one amino acid of a protein: the second is the acceptance of the mutation by the species as the new predominant form. To be accepted,

> the new amino acid usually must function in a way similar to the old one: chemical and physical similarities are found between the amino acids that are observed to interchange frequently (Dayhoff et al. 1978: 345).

Given the classification of point mutations in chapter 4, at the protein level, an accepted point mutation is hence usually either a silent mutation or a synonymous missense mutation; consequently, at the DNA level, an accepted point mutation is usually a substitution. Put differently, since frameshift mutations are usually deleterious, deletions and insertions are usually not accepted by natural selection. However, as I shall argue below, it is incorrect to equate accepted point mutations with accepted substitutions.

I now turn to the construction of PAM matrices. A quick word on notation: PAM1, PAM200, PAMn matrices are PAM matrices with an evolutionary distance of 1, 200, n PAM units. Consider first the PAM1 mutation probability matrix $\mathbf{P}$ as shown in Figure 6.10. Here an element $\mathbf{p}_{\mathsf{a},\mathsf{a}'} \in \mathbf{P}$ denotes the probability that an amino acid a' is replaced by an amino acid a in one PAM. $\mathbf{P}$ is constructed as follows (adapted from Dayhoff et al. 1978: 348):

$$\mathbf{p}_{\mathsf{a},\mathsf{a}'} = \begin{cases} \dfrac{\theta \times m(\mathsf{a}') \times \mathbf{n}_{\mathsf{a},\mathsf{a}'}}{\sum\limits_{\mathsf{a}'' \in A} \mathbf{n}_{\mathsf{a}'',\mathsf{a}'}} & \text{if } \mathsf{a} \neq \mathsf{a}' \\ 1 - \theta \times m(\mathsf{a}') & \text{otherwise} \end{cases} \tag{6.71}$$

where:

- A is the set of amino acids. I will use a with or without index as variable to range over A.[2]
- $\mathbf{N}$ is a 20×20 symmetric real matrix with the amino acids as rows and columns where each element $\mathbf{n}_{\mathsf{a},\mathsf{a}'} \in \mathbf{N}$ denotes the number of observed accepted point mutations involving the amino acids a, a' as shown in Figure 6.11. Dayhoff et al. base $\mathbf{N}$ on an analysis of "closely related sequences from 34 [protein] superfamilies" (1978: 346) from which they assemble 71 phylogenetic trees under maximum parsimony (henceforth referred to as their dataset). For each tree, the accepted point mutations can then be read off from parent/child pairs.

[2] I do not use Φ and p, q as introduced in the language describing the simple model (see definition 5.2) to refer to the set of amino acids respectively arbitrary amino acids in order to distinguish the mathematical model family of PAM from logical models.

ORIGINAL AMINO ACID

REPLACEMENT AMINO ACID	A Ala	R Arg	N Asn	D Asp	C Cys	Q Gln	E Glu	G Gly	H His	I Ile	L Leu	K Lys	M Met	F Phe	P Pro	S Ser	T Thr	W Trp	Y Tyr	V Val
A Ala	9867	2	9	10	3	8	17	21	2	6	4	2	6	2	22	35	32	0	2	18
R Arg	1	9913	1	0	1	10	0	0	10	3	1	19	4	1	4	6	1	8	0	1
N Asn	4	1	9822	36	0	4	5	6	21	3	1	13	0	1	2	20	9	1	4	1
D Asp	6	0	42	9859	0	6	53	6	4	1	0	3	0	0	1	5	3	0	0	1
C Cys	1	1	0	0	9973	0	0	0	1	1	0	0	0	0	1	5	1	0	3	2
Q Gln	3	9	4	5	0	9876	27	1	23	1	3	6	4	0	6	2	2	0	0	1
E Glu	10	0	7	56	0	35	9865	4	2	3	1	4	1	0	3	4	2	0	1	2
G Gly	21	1	12	11	1	3	7	9935	1	0	1	2	1	1	3	21	3	0	0	5
H His	1	8	18	3	1	20	1	0	9912	0	1	1	0	2	3	1	1	1	4	1
I Ile	2	2	3	1	2	1	2	0	0	9872	9	2	12	7	0	1	7	0	1	33
L Leu	3	1	3	0	0	6	1	1	4	22	9947	2	45	13	3	1	3	4	2	15
K Lys	2	37	25	6	0	12	7	2	2	4	1	9926	20	0	3	8	11	0	1	1
M Met	1	1	0	0	0	2	0	0	0	5	8	4	9874	1	0	1	2	0	0	4
F Phe	1	1	1	0	0	0	0	1	2	8	6	0	4	9946	0	2	1	3	28	0
P Pro	13	5	2	1	1	8	3	2	5	1	2	2	1	1	9926	12	4	0	0	2
S Ser	28	11	34	7	11	4	6	16	2	2	1	7	4	3	17	9840	38	5	2	2
T Thr	22	2	13	4	1	3	2	2	1	11	2	8	6	1	5	32	9871	0	2	9
W Trp	0	2	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	9976	1	0
Y Tyr	1	0	3	0	3	0	1	0	4	1	1	0	0	21	0	1	1	2	9945	1
V Val	13	2	1	1	3	2	2	3	3	57	11	1	17	1	3	2	10	0	2	9901

Figure 6.10

PAM1 mutation probability matrix $\mathbf{P}$ (Dayhoff et al. 1978: 348). An element $\mathbf{p}_{\mathsf{a},\mathsf{a}'} \in \mathbf{P} \times 10^{-4}$ is the probability that an amino acid a' is replaced by an amino acid a in one PAM. For example, $\mathbf{p}_{\mathsf{A},\mathsf{A}} \times 10^{-4} = 0.9867$ is the probability that alanine is replaced by alanine in one PAM; $\mathbf{p}_{\mathsf{A},\mathsf{R}} \times 10^{-4} = 0.0001$ is the probability that alanine is replaced by arginine in one PAM.

- $m : A \to \mathbb{R}$ is a function which assigns to each amino acid its relative mutability as per Table 6.2. With respect to the dataset of Dayhoff et al., for an amino acid $\mathsf{a} \in A$, $m(\mathsf{a})$ denotes:

$$\frac{\text{number of mutations involving } \mathsf{a}}{\text{number of occurences of } \mathsf{a}} \tag{6.72}$$

- θ is a proportionality constant. The number of amino acids per 100 amino acids that are not replaced in $\mathbf{P}$ is 99. This is expressed by (Dayhoff et al. 1978: 348):

$$100 \times \sum_{\mathsf{a} \in A} f(\mathsf{a}) \times \mathbf{p}_{\mathsf{a},\mathsf{a}} = 99 \tag{6.73}$$

  where $f : A \to \mathbb{R}$ is a function that assigns to each amino acid its relative frequency as per Table 6.2. With respect to the dataset of Dayhoff et al., $f(\mathsf{a})$ denotes:

$$\frac{\text{number of occurences of } \mathsf{a}}{\text{sum of occurences of all amino acids}} \tag{6.74}$$

  By (6.71), (6.73) reduces to:

$$100 \times \sum_{\mathsf{a} \in A} f(\mathsf{a}) \times (1 - \theta \times m(\mathsf{a})) = 99 \tag{6.75}$$

  By solving (6.75) for θ, we have $\theta \approx 0.000133$.[3]

So a non-diagonal element $\mathbf{p}_{\mathsf{a},\mathsf{a}'} \in \mathbf{P}$ denotes the probability that an amino acid a' is replaced by an amino acid a in one PAM. By contrast, a diagonal element $\mathbf{p}_{\mathsf{a},\mathsf{a}} \in \mathbf{P}$ denotes the probability that the amino acid a is not replaced in one PAM. Consider two numerical examples. The non-diagonal element $\mathbf{p}_{\mathsf{A},\mathsf{E}}$ denotes the probability that E is replaced by A in one PAM:

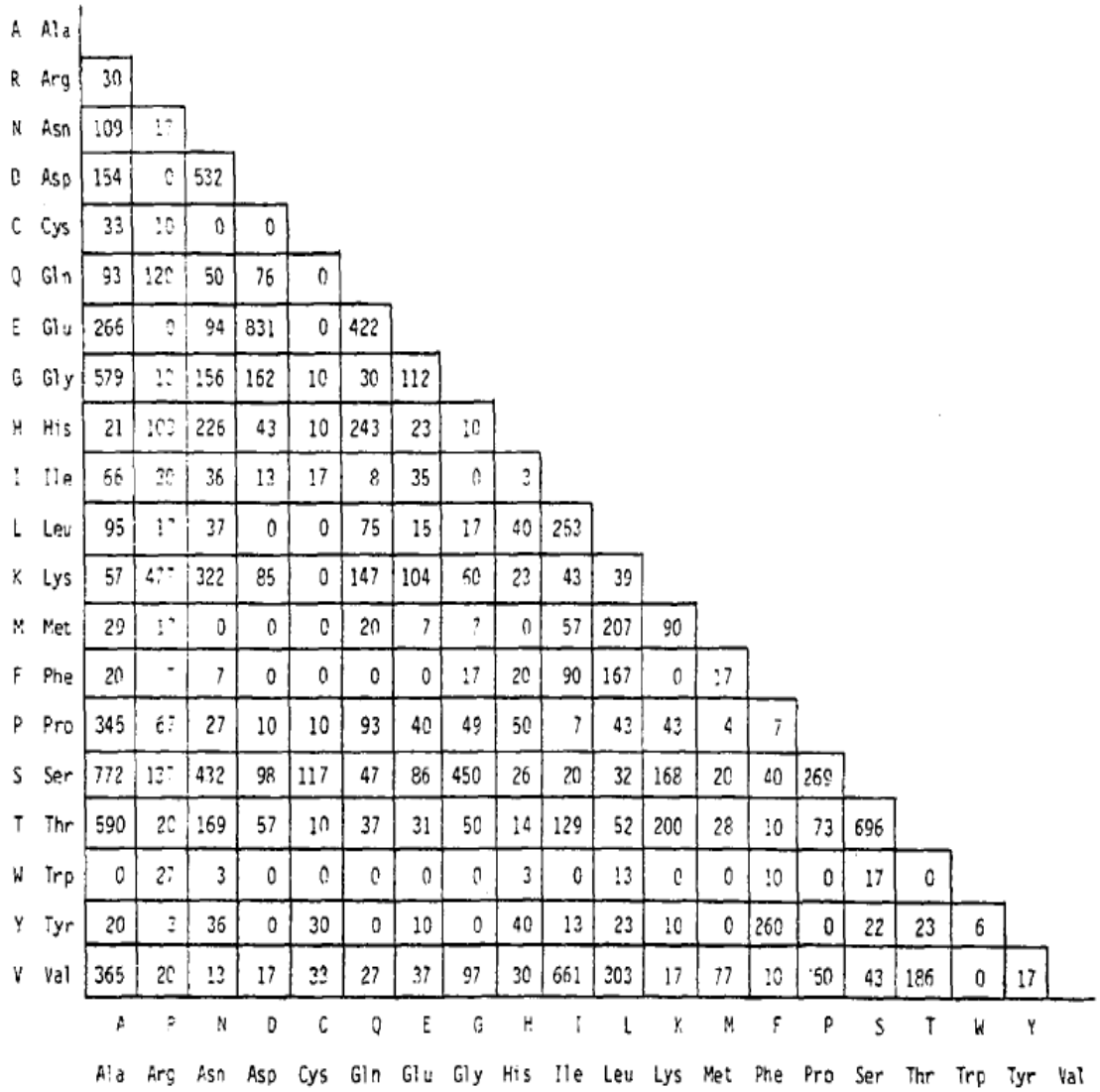
$$\mathbf{p}_{\mathsf{A},\mathsf{E}} = \frac{\theta \times m(\mathsf{E}) \times \mathbf{n}_{\mathsf{A},\mathsf{E}}}{\sum_{\mathsf{a} \in A} \mathbf{n}_{\mathsf{a},\mathsf{E}}} = \frac{0.000133 \times 102 \times 42.2}{211} = 0.0017 \tag{6.76}$$

The diagonal element $a_{\mathsf{E},\mathsf{E}}$ denotes the probability that E is not replaced in one PAM:

$$\mathbf{p}_{\mathsf{E},\mathsf{E}} = 1 - \theta \times m(\mathsf{E}) = 1 - 0.000133 \times 102 = 0.9865 \tag{6.77}$$

Higher-level PAM mutation probability matrices can then be derived from the PAM1

[3] The solution is approximate since some elements of $\mathbf{N}$ are illegible in the only obtainalble copy of Dayhoff et al. (1978).



		A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	Ala																				
R	Arg	30																			
N	Asn	109	17																		
D	Asp	154	0	532																	
C	Cys	33	10	0	0																
Q	Gln	93	120	50	76	0															
E	Glu	266	0	94	831	0	422														
G	Gly	579	10	156	162	10	30	112													
H	His	21	100	226	43	10	243	23	10												
I	Ile	66	20	36	13	17	8	35	0	3											
L	Leu	95	17	37	0	0	75	15	17	40	253										
K	Lys	57	477	322	85	0	147	104	60	23	43	39									
M	Met	29	17	0	0	0	20	7	7	0	57	207	90								
F	Phe	20	7	7	0	0	0	0	17	20	90	167	0	17							
P	Pro	345	67	27	10	10	93	40	49	50	7	43	43	4	7						
S	Ser	772	137	432	98	117	47	86	450	26	20	32	168	20	40	269					
T	Thr	590	20	169	57	10	37	31	50	14	129	52	200	28	10	73	696				
W	Trp	0	27	3	0	0	0	0	0	3	0	13	0	0	10	0	17	0			
Y	Tyr	20	3	36	0	30	0	10	0	40	13	23	10	0	260	0	22	23	6		
V	Val	365	20	13	17	33	27	37	97	30	661	303	17	77	10	50	43	186	0	17	

Figure 6.11

Matrix $\mathbf{N}$ of the number observed accepted point mutations in the dataset (Dayhoff et al. 1978: 346). An element $\mathbf{n}_{\mathsf{a},\mathsf{a}'} \in \mathbf{N} \times 10^{-1}$ is the number of observed accepted point mutations resulting in a change from amino acid a' to amino acid a or from a to a'. Fractions are due to ambiguous parent nodes in the dataset.

a	$m(\mathsf{a})$	$f(\mathsf{a})$	a	$m(\mathsf{a})$	$f(\mathsf{a})$
A	100	0.087	L	40	0.085
R	65	0.041	K	56	0.081
N	134	0.04	M	94	0.015
D	106	0.047	F	41	0.04
C	20	0.033	P	56	0.051
Q	93	0.038	S	120	0.07
E	102	0.05	T	97	0.058
G	49	0.089	W	18	0.01
H	66	0.034	Y	41	0.03
I	96	0.037	V	74	0.065

Table 6.2
Relative mutabilities and frequencies (with respect to the dataset) of the amino acids (Dayhoff et al. 1978: 347).

mutation probability matrix by matrix multiplication (Dayhoff et al. 1978: 349f.):

$$\mathrm{PAM}n = \mathrm{PAM1}^n = \mathbf{P}^n = \underbrace{\mathbf{P} \times \cdots \times \mathbf{P}}_{n} \tag{6.78}$$

With PAM mutation probability matrices in place, I now construct a probabilistic model which I will call 'Dayhoff model'. The main idea here is to define the probability function of the Dayhoff model based on the PAM1 mutation probability matrix $\mathbf{P}$. This requires a reinterpretation of the probability function, however. To see this, recall two things:

1. The probability function in the probabilistic model is interpreted as the conditional probability of reaching some codon via single substitution (see definition 6.2).
2. A point accepted mutation is usually a single substitution (see above). However, there are some elements $\mathbf{p}_{\mathsf{a},\mathsf{a}'} \in \mathbf{P}$ such that $\mathbf{p}_{\mathsf{a},\mathsf{a}'} > 0$ even though it is impossible that the replacement of amino acid a' with amino acid a was caused by a single substitution. That is, some accepted point mutations observed in the dataset of Dayhoff et al. cannot be single substitutions or even point mutations; see Table 6.3 for examples of such mismatches with respect to glutamate.

In order resolve this tension, there are two options: Either clean the dataset such as to exclude all mutations that are not caused by single substitutions or reinterpret the probability function as the conditional probability of reaching some codon via an accepted point mutation. The first option is not feasible for practical and theoretical considera-

tions. This leaves open the second option:

Definition 6.5 (Dayhoff model)
The Dayhoff model is a probabilistic model $\mathfrak{M}^{\mathfrak{D}} = \left\langle C^{\mathfrak{D}}, P^{\mathfrak{D}}, \Phi^{\mathfrak{D}}, V^{\mathfrak{D}} \right\rangle$ where:

- $C^{\mathfrak{D}}, \Phi^{\mathfrak{D}}, V^{\mathfrak{D}}$ are standard (see definition 6.2).
- $P^{\mathfrak{D}} : C^{\mathfrak{D}} \times C^{\mathfrak{D}} \to \mathbb{R}$ is a conditional probability function interpreted as accepted point mutation. The probability that $c' \in C^{\mathfrak{D}}$ can be reached from $c \in C^{\mathfrak{D}}$ via an accepted point mutation is written as $P^{\mathfrak{D}}(c'|c)$ and given by:

$$P^{\mathfrak{D}}(c'|c) = \begin{cases} \mathbf{p}_{\mathsf{a},\mathsf{a}'} & \text{if } c' \in V^{\mathfrak{D}}(\mathsf{a}) \text{ and } c \in V^{\mathfrak{D}}(\mathsf{a}') \\ 0 & \text{otherwise} \end{cases} \tag{6.79}$$

  where $c, c' \in C^{\mathfrak{D}}$, $\mathbf{p}_{\mathsf{a},\mathsf{a}'} \in \mathbf{P}$ and $\mathsf{a}, \mathsf{a}' \in A$.

So in contrast to a probabilistic model, the probability function in the Dayhoff model is interpreted as accepted point mutation rather than as single substitution. It is easy to see that the probability function adheres to the constraints (6.43) and (6.44) since it is defined terms of the PAM1 mutation probability matrix.

From the reinterpretation of the probability function and 6.79 follows that each block of codons in the partition induced by the valuation $V^{\mathfrak{D}}$ constitutes a bisimilarity class in $\mathfrak{D}$:

$$\text{If } c \in V^{\mathfrak{D}}(p), \text{ then } \|c\| = V^{\mathfrak{D}}(p) \tag{6.80}$$

where $c \in C^{\mathfrak{D}}$ and $p \in \Phi^{\mathfrak{D}}$. In other words, all p-codons are such that they exactly match the probabilities and types of codons that can be reached via accepted point mutations in the Dayhoff model. This result is not surprising since the probability function is based on the PAM1 mutation probability matrix; in turn, this matrix is based on observations of changes in amino acids. Put differently, we had seen in chapter 5 that the simple model encodes the DNA level via its frame and the protein level via its valuation; the same holds true for probabilistic models. The Dayhoff model is distinguished from the simple model and other probabilistic models in that the DNA level does not matter since all p-codons are lumped together.

I will now employ bisimilarity contraction in oder to make this observation more precise; this has the added benefit of significantly reducing the complexity of the Dayhoff model.

a	$\mathbf{p}_{\mathsf{a},\mathsf{E}} > 0$	$c_{\mathsf{E}} R c_{\mathsf{a}}$	a	$\mathbf{p}_{\mathsf{a},\mathsf{E}} > 0$	$c_{\mathsf{E}} R c_{\mathsf{a}}$
A	✓	✓	L	✓	✗
R	✗	✗	K	✓	✓
N	✓	✗	M	✗	✗
D	✓	✓	F	✗	✗
C	✗	✗	P	✓	✗
Q	✓	✓	S	✓	✗
E	✓	✓	T	✓	✗
G	✓	✓	W	✗	✗
H	✓	✗	Y	✓	✗
I	✓	✗	V	✓	✓

Table 6.3

Mismatches between the PAM1 mutation probability matrix $\mathbf{P}$ and the simple model $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ with respect to replacements of glutamate E. Here a is an amino acid, $\mathbf{p}_{\mathsf{a},\mathsf{E}} \in \mathbf{P}$, and $c_{\mathsf{a}} \in C$ is an a-codon such that $c_{\mathsf{E}} R c_{\mathsf{a}}$ expresses that in the simple model, an E-codon can be reached via single substitution from an a-codon. For example, there is a none-zero probability that E is replaced with N according to $\mathbf{P}$ whereas this is impossible in the simple model.

Consider the definition of the small Dayhoff model:

Definition 6.6 (Small Dayhoff model)

The small Dayhoff model is a probabilistic model $\mathfrak{X} = \left\langle C^{\mathfrak{X}}, P^{\mathfrak{X}}, \Phi^{\mathfrak{X}}, V^{\mathfrak{X}} \right\rangle$ where:

- $C^{\mathfrak{X}}$ is the set of bisimilarity classes of $\|c\|$ of codons $c \in C^{\mathfrak{D}}$.
- $P^{\mathfrak{X}}$ is a conditional probability function such that $P^{\mathfrak{X}}(\|c'\| \| \|c\|) = \alpha$ if there are $c \in \|c\|$ and $c' \in \|c\|$ such that $P^{\mathfrak{D}}(c'|c) = \alpha$.
- $\Phi^{\mathfrak{X}} = \Phi^{\mathfrak{D}}$.
- $V^{\mathfrak{X}} : \Phi^{\mathfrak{X}} \to C^{\mathfrak{X}}$ is a valuation function such that $\|c\| \in V^{\mathfrak{X}}(p)$ if $c \in V^{\mathfrak{D}}(p)$.

Note that by (6.80), $C^{\mathfrak{X}}$ can be interpreted as the set of amino acids without loss of generality. The extended probabilistic amino acid language can be used to describe the small Dayhoff model. The most important observation is (for $p = \mathsf{a}$ and $p' = \mathsf{a}'$):

$$\text{If } \|c\| \in V^{\mathfrak{X}}(p'), \text{ then } \mathfrak{X}, \|c\| \Vdash \otimes^m p = \mathbf{p}_{\mathsf{a},\mathsf{a}'} \in \mathbf{P}^m \tag{6.81}$$

That is, the m-th level probability of reaching a p-codon from a p'-codon is in the (small) Dayhoff model is the probability given by the PAMm mutation probability matrix for replacing the amino acid a' with the amino acid a. Therefore, all PAM mutation probability matrices are fully captured by the (small) Dayhoff model and the extended probabilistic amino acid language via the $\circledast^m$-modality.

6.4 Summary

I extend the simple model and language to account for comparative (historical) biological possibility. This yields a ranking of hemoglobin variants $v, v', \ldots$ caused by single substitutions at codon 6 of the hemoglobin beta gene. I distinguish four circumstances under which v is more possible than v': (1) v is easier to bring about that v', implemented by a modal operator capturing Hamming distance. (2) There are more possible v than v', implemented by a modal operator counting variants. (3) There are more ways to realize v than v', implemented by a modal operator counting unique sequences of single substitutions. (4) v is more probable than v', implemented by a non-epistemic probabilistic modal operator and a weighted binary relation interpreted as single substitution. In addition, I discuss the conditions for the introduced modal operators' loss of historical or local context, and I show the extension's ability to incorporate transition/transversion bias or amino acid scoring matrices.

7. Generalized model

In this chapter, I will outline how the modeling restrictions imposed in chapter 4 can be lifted in order to provide logical models of any variant caused by any point mutation at the coding region of any gene. In section 7.1, I will show that these restriction can be lifted via a generalization of the simple model. In section 7.2, I will discuss a number of limitations of the generalized model.

7.1 Lifting modeling restrictions via generalization

All logical models so far presented in chapters 5 and 6 are restricted to variants of HbA caused by single substitutions at codon 6 of *HBB* as defined in chapter 4. To wit, there are three restrictions to be lifted:

1. The restriction to variants of HbA caused by single substitutions at codon 6 of *HBB*.
2. The restriction to variants of HbA caused by single substitutions at codon 6 of *HBB*.
3. The restriction to variants of HbA caused by single substitutions at codon 6 of *HBB*.

Getting rid of the first restriction comes for free: As pointed out in section 5.2, the simple model is a non-specific model of HbA variants caused by single substitutions at codon 6 of *HBB*. That is, the simple model does not encode any empirical information specific to either codon 6 or *HBB* such as upstream or downstream context. The same holds for the other models discussed in chapters 5 and 6.

By contrast, lifting the second and the third restriction can be achieved to some extent via a generalization of the simple model:

Definition 7.1 (Generalized model)
A generalized model $\mathfrak{M}^{\mathfrak{G}}$ is a quintuple $\left\langle G^{\mathfrak{G}}, M^{\mathfrak{G}}, R_{\mu}^{\mathfrak{G}}, \Phi^{\mathfrak{G}}, V^{\mathfrak{G}} \right\rangle$ such that:

- $G^{\mathfrak{G}}$ is the set of genes. A gene $g \in G^{\mathfrak{G}}$ is represented as string over the alphabet $\{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}$.
- For each class of point mutation $\mu \in M^{\mathfrak{G}} = \{\text{substitution}, \text{deletion}, \text{insertion}\}$, $R_{\mu}^{\mathfrak{G}} \subseteq G^{\mathfrak{G}} \times G^{\mathfrak{G}}$ is a binary relation interpreted as single substitution, deletion and insertion respectively.
- $\Phi^{\mathfrak{G}}$ is the set of atomic propositions interpreted as the set of proteins. The lowercase letters $p, q, \ldots$ range over Φ.
- $V^{\mathfrak{G}} : \Phi^{\mathfrak{G}} \to \mathcal{P}(G^{\mathfrak{G}})$ is a valuation which assigns to each atomic proposition $p \in \Phi^{\mathfrak{G}}$ some set of genes $V^{\mathfrak{G}}(p) \subseteq G^{\mathfrak{G}}$. Intuitively, the valuation indicates which genes code for which proteins.

Similar to the simple model, I will only be concerned with an empirically adequate valuation. It is instructive to spell out further similarities and differences between the generalized model $\mathfrak{M}^{\mathfrak{G}}$ and the simple model $\mathfrak{M}$:

- The domain of $\mathfrak{M}^{\mathfrak{G}}$ consists of genes whereas the domain of $\mathfrak{M}$ consists of codons; the domain of the former is hence larger than the domain of the latter by several orders of magnitude. The domain of $\mathfrak{M}^{\mathfrak{G}}$ is still finite, however.
- In contrast to $\mathfrak{M}$, $\mathfrak{M}^{\mathfrak{G}}$ not only contains a binary relation interpreted as single substitution, but also a binary relation for single deletion and one for single insertion. Note that single substitution is symmetric whereas both single deletion and single insertion are antisymmetric.
- The atomic propositions of $\mathfrak{M}^{\mathfrak{G}}$ are strings over the set of atomic propositions of $\mathfrak{M}$.
- Similar to $\mathfrak{M}$, the DNA level in $\mathfrak{M}^{\mathfrak{G}}$ is encoded in the frame whereas the protein level is encoded in the valuation. Again, there is exactly one empirically adequate valuation, namely the valuation which assigns to each gene the protein it actually codes for; all other valuations will be neglected. The resulting empirically adequate generalized model I call the generalized model.

Furthermore, consider briefly the differences and similarities between the generalized model $\mathfrak{M}^{\mathfrak{G}}$ and the Library of Mendel $\langle \Sigma_{\mathrm{M}}, R_{\mathrm{M}} \rangle$ discussed in chapter 3:

- The domain of $\mathfrak{M}^{\mathfrak{G}}$ consists of genes whereas the domain of $\langle \Sigma_{\mathrm{M}}, R_{\mathrm{M}} \rangle$ consists of genomes; the former is finite whereas the latter is countably infinite (see section 3.3).
- The binary relation of $\mathfrak{M}^{\mathfrak{G}}$ is interpreted and well-defined whereas the binary relation of $\langle \Sigma_{\mathrm{M}}, R_{\mathrm{M}} \rangle$ is not (see section 3.4.1).

I now turn to the definition of the basic protein language.

Definition 7.2 (Basic protein language)
Generalized models $\mathfrak{M}^{\mathfrak{G}} = \left\langle G^{\mathfrak{G}}, M^{\mathfrak{G}}, R_{\mu}^{\mathfrak{G}}, \Phi^{\mathfrak{G}}, V^{\mathfrak{G}} \right\rangle$ are described via the basic protein language $\mathcal{L}^{\mathcal{G}}$. The syntax of $\mathcal{L}^{\mathcal{G}}$ is given by the following Backus-Naur form:

$$\phi \;:=\; p \mid \neg\phi \mid \phi \vee \phi \mid \;\Diamond_{\mu}\, \phi$$

where $p \in \Phi^{\mathfrak{G}}$ and $\mu \in M^{\mathfrak{G}}$. The standard abbreviations for the classical connectives $\wedge, \rightarrow, \leftrightarrow$ are used; in addition, it is convenient to use:

$$\Box_{\mu}\phi \;:=\; \neg \Diamond_{\mu} \neg\phi \tag{7.1}$$

$$\langle M \rangle \phi \;:=\; \Diamond_{\mu_1} \vee \cdots \vee \Diamond_{\mu_n} \phi \tag{7.2}$$

$$[M]\phi \;:=\; \neg\langle M \rangle \neg\phi \tag{7.3}$$

where $n = |M^{\mathfrak{G}}|$. That a formula ϕ of $\mathcal{L}^{\mathcal{G}}$ is true in $\mathfrak{M}^{\mathfrak{G}}$ at a gene $g \in G^{\mathfrak{G}}$ is written as $\mathfrak{M}^{\mathfrak{G}}, g \Vdash \phi$. The semantics of $\mathcal{L}^{\mathcal{G}}$ are given recursively:

$$\mathfrak{M}^{\mathfrak{G}}, g \Vdash p \text{ iff } c \in V^{\mathfrak{G}}(p) \tag{7.4}$$

$$\mathfrak{M}^{\mathfrak{G}}, g \Vdash \neg\phi \text{ iff not } \mathfrak{M}^{\mathfrak{G}}, g \Vdash \phi \tag{7.5}$$

$$\mathfrak{M}^{\mathfrak{G}}, g \Vdash \phi \vee \psi \text{ iff } \mathfrak{M}^{\mathfrak{G}}, g \Vdash \phi \text{ or } \mathfrak{M}^{\mathfrak{G}}, g \Vdash \phi \tag{7.6}$$

$$\mathfrak{M}^{\mathfrak{G}}, g \Vdash \Diamond_{\mu}\phi \text{ iff } \mathfrak{M}^{\mathfrak{G}}, g' \Vdash \phi \text{ for some } g' \in G \text{ such that } g R_{\mu}^{\mathfrak{G}} g' \tag{7.7}$$

The literal meaning of $\Diamond_{\mu}\phi$ is that a ϕ-codon can be reached via a single μ point mutation. The intended meaning of $\Diamond_{\mu}\phi$ is that ϕ is possible via a single μ point mutation. The literal meaning of $\langle M \rangle \phi$ is that a ϕ-codon can be reached via a single point mutation. Put differently, the (redundant) explicit semantics of the $\langle M \rangle$-modality are:

$$\mathfrak{M}^{\mathfrak{G}}, g \Vdash \langle M \rangle \phi \text{ iff } \exists g' \in G \text{ s.t. } \mathfrak{M}^{\mathfrak{G}}, g' \Vdash \phi \text{ and } g R^{\mathfrak{G}} g' \text{ where } R^{\mathfrak{G}} = \bigcup_{\mu \in M^{\mathfrak{G}}} R_{\mu}^{\mathfrak{G}} \tag{7.8}$$

The intended meaning of $\langle M \rangle \phi$ is that ϕ is possible via a single point mutation.

With the generalized model and the basic protein language in place, it is straightforward to see how the second and third restriction can be lifted. I will take these in turn: The second restriction, namely the restriction to single substitutions, is lifted in the generalized model by introducing a binary relation for each of the three classes of point mutations. This is mirrored in the multimodal basic protein language which caters for possibility via single substitution, single deletion, single insertion or single point mutation tout court. The third restriction, namely the restriction to codon 6 of *HBB*, is lifted since the domain of the generalized model contains any gene and is not limited to a specific codon. A final restriction was to understand 'caused' as 'fully caused' (see section 4); this restriction was intended to exclude multiple point mutations. This restriction is lifted by treating such mutations as serialized occurrences of single point mutations whilst neglecting their ordering. This is unproblematic in most cases, however, there are exceptions; see the next subsection on the distinction between opaque and transparent modalities for details on how to deal with these exceptions.

For illustration, consider two examples. Figure 7.1 depicts the (partial) generalized model of known variants of HbA caused by single point mutations at codon 6 of *HBB* (see Table 4.1). Figure 7.2 depicts the (partial) generalized model of HbRothschild, HbArlingtonPark and HbC-Rothschild each of which are caused by a combination of multiple point mutations at *HBB*.

To sum up, I have shown that the modeling restrictions imposed in chapter 4 can all be lifted are hence abstractions rather than idealizations in the sense of Stokhof and van Lambalgen (2011). That is, while the generalized model is much less tractable than the simple model, it retains all other (especially conceptual) results, as wanted.

7.2 Limitations

In this section, a number of limitations of the generalized model and the basic protein language are discussed. In subsection 7.2.1, I will show how the limited expressive power of the basic protein language can be increased. In subsection 7.2.2, I will touch upon the distinction between opaque and transparent modalities.

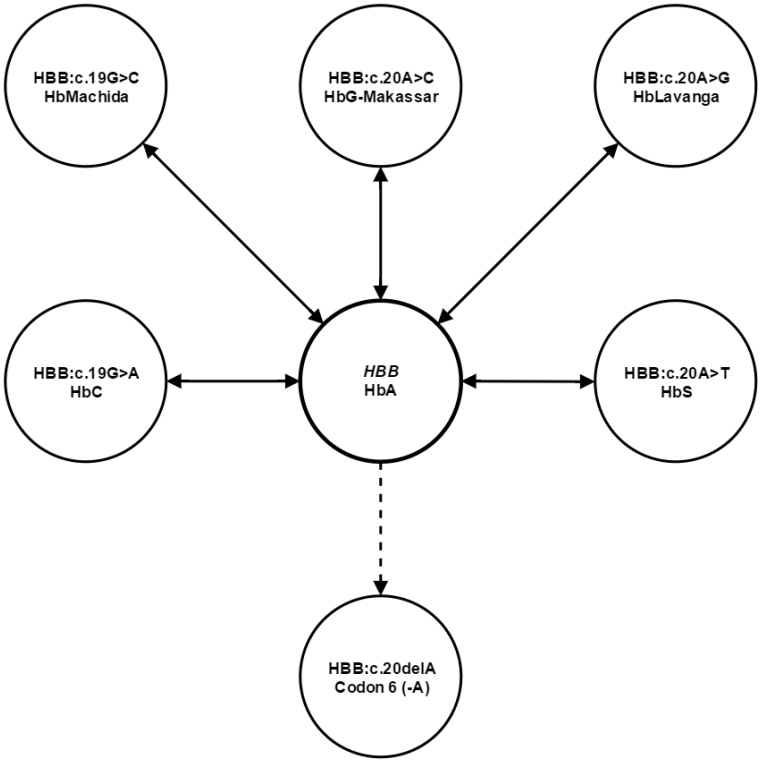
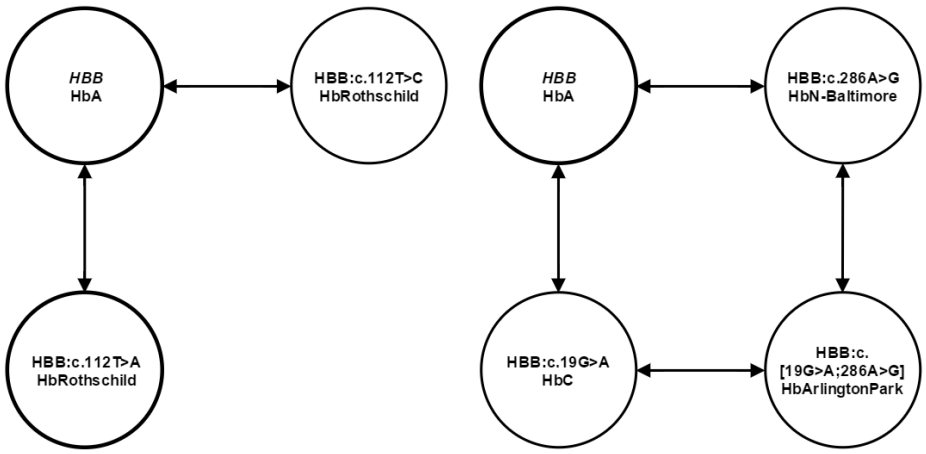
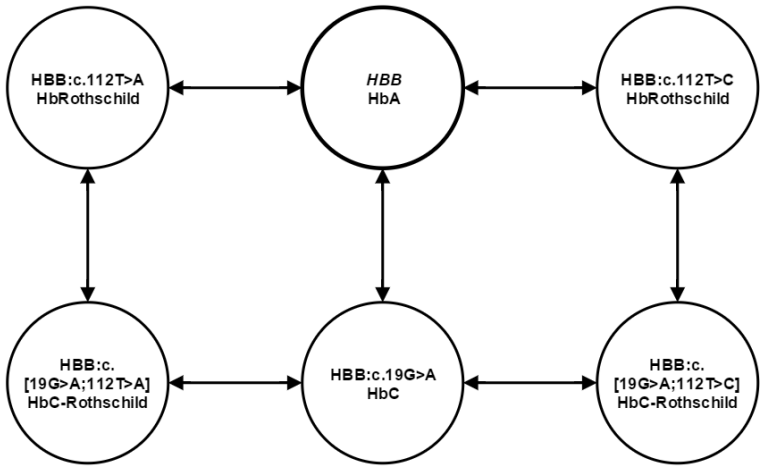


Figure 7.1

The (partial) generalized model $\mathfrak{M}^{\mathfrak{G}}$ of the known HbA variants caused by single point mutations at codon 6 of *HBB* represented as directed graph. Full arrows represent substitution, dashed arrows represent deletion.



(a) HbRothschild **(b)** HbArlingtonPark



(c) HbC-Rothschild

Figure 7.2

The (partial) generalized models of HbA variants caused by multiple point mutations at *HBB* represented as directed graphs. (a) HbRothschild is caused by a substitution of thymine with either adenine or cytosine at codon 37. (b) HbArlingtionPark is caused by a substitution of both guanine with adenine at codon 6 and adenine with guanine at codon 95. (c) HbC-Rothschild is caused by a substitution of both guanine with adenine at codon 6 and thymine with either adenine or cytosine at codon 37. Note that according to the generalized model, HbC-Rotschild is possible at *HBB* only at the second level.

7.2.1 Expressiveness

The basic protein language is limited in that it is a propositional modal language. It is well conceivable that more expressive power is needed, for example to distinguish between what is biologically possible de re versus what is biologically possible de dicto (see section 2.1). In what follows, I will outline a first-order modal language based on the framework of Blackburn and van Benthem (2007: 66ff.). In order to do so, I start with the definition of a first-order generalized model:

Definition 7.3 (First-order generalized model)
A first-order generalized model $\mathfrak{M}^{\mathfrak{F}}$ is a septuple $\left\langle G^{\mathfrak{F}}, M^{\mathfrak{F}}, R_{\mu}^{\mathfrak{F}}, D^{\mathfrak{F}}, N^{\mathfrak{F}}, \Pi^{\mathfrak{F}}, V_{g}^{\mathfrak{F}} \right\rangle$ such that:

- $G^{\mathfrak{F}} = G^{\mathfrak{G}}$, $M^{\mathfrak{F}} = M^{\mathfrak{G}}$, and $R_{\mu}^{\mathfrak{F}} = R_{\mu}^{\mathfrak{G}}$.
- $D^{\mathfrak{F}}$ is the domain of quantification interpreted as the set of proteins. The lowercase letters x, y with or without subscript range over $D^{\mathfrak{F}}$.
- $N^{\mathfrak{F}}$ is the set of names of proteins such as alpha globin or beta globin.
- $\Pi^{\mathfrak{F}}$ is the set of n-ary predicates $P(t_1, \ldots, t_n)$ where t with or without subscript is a term (that is, name or variable).
- $V_{g}^{\mathfrak{F}}$ is a valuation function for each $g \in G^{\mathfrak{F}}$ such that:

$$V_{g}^{\mathfrak{F}}(\xi) = \begin{cases} d \in D^{\mathfrak{F}} & \text{if } \xi \in N^{\mathfrak{F}} \\ S \subseteq (D^{\mathfrak{F}})^{n} & \text{if } \xi \in \Pi^{\mathfrak{F}} \end{cases} \tag{7.9}$$

  Intuitively, the valuation function maps proteins to names and subsets of the n-fold Cartesian product of D to n-ary predicates at each gene.

Again, I am exclusively concerned with empirically adequate valuations. In addition, I have assumed that the domain of quantification is constant (instead of independent or varying, see Girle 2003: 60–63 for an overview) across genes in the first-order generalized model.

I now turn to the definition of the first-order protein language:

Definition 7.4 (First-order protein language)
First-order generalized models $\mathfrak{M}^{\mathfrak{F}} = \left\langle G^{\mathfrak{F}}, M^{\mathfrak{F}}, R_{\mu}^{\mathfrak{F}}, D^{\mathfrak{F}}, N^{\mathfrak{F}}, \Pi^{\mathfrak{F}}, V_g^{\mathfrak{F}} \right\rangle$ are described via the first-order protein language $\mathcal{L}^{\mathcal{F}}$. The syntax of $\mathcal{L}^{\mathcal{F}}$ is given by the following Backus-Naur form:

$$\phi \;:=\; P(t_1, \ldots, t_n) \mid t = t' \mid \neg\phi \mid \phi \vee \phi \mid \; \Diamond_{\mu}\, \phi \mid \exists x \phi$$

where $P(t_1, \ldots, t_n) \in \Pi^{\mathfrak{F}}$, and $\mu \in M^{\mathfrak{F}}$. The standard abbreviations for the classical connectives $\wedge, \rightarrow, \leftrightarrow$ are used; in addition to $\Box_{\mu}$, $\langle M \rangle$, and $[M]$ as per definition 7.1, it is convenient to use:

$$\forall x \phi \;:=\; \neg \exists x \neg \phi \tag{7.10}$$

Let $\bullet$ be an assignment such that:

$$\bullet(t) = \begin{cases} V_g^{\mathfrak{F}}(t) & \text{if } t \in N^{\mathfrak{F}} \\ d \in D^{\mathfrak{F}} & \text{otherwise} \end{cases} \tag{7.11}$$

That a formula ϕ of $\mathcal{L}^{\mathcal{F}}$ is true in $\mathfrak{M}^{\mathfrak{F}}$ under assignment $\bullet$ at gene $g \in G^{\mathfrak{F}}$ is written as $\mathfrak{M}^{\mathfrak{F}}, \bullet, g \Vdash \phi$. The semantics of $\mathcal{L}^{\mathcal{F}}$ are given recursively:

$$\mathfrak{M}^{\mathfrak{F}}, \bullet, g \Vdash P(t_1, \ldots, t_n) \text{ iff } \langle \bullet(t_1), \ldots, \bullet(t_n) \rangle \in V_g^{\mathfrak{F}}(P) \tag{7.12}$$

$$\mathfrak{M}^{\mathfrak{F}}, \bullet, g \Vdash t = t' \text{ iff } \bullet(t) = \bullet(t') \tag{7.13}$$

$$\mathfrak{M}^{\mathfrak{F}}, \bullet, g \Vdash \neg\phi \text{ iff not } \mathfrak{M}^{\mathfrak{F}}, \bullet, g \Vdash \phi \tag{7.14}$$

$$\mathfrak{M}^{\mathfrak{F}}, \bullet, g \Vdash \phi \vee \psi \text{ iff } \mathfrak{M}^{\mathfrak{F}}, \bullet, g \Vdash \phi \text{ or } \mathfrak{M}^{\mathfrak{F}}, \bullet, g \Vdash \phi \tag{7.15}$$

$$\mathfrak{M}^{\mathfrak{F}}, \bullet, g \Vdash \Diamond_{\mu}\phi \text{ iff } \mathfrak{M}^{\mathfrak{F}}, \bullet, g' \Vdash \phi \text{ for some } g' \in G^{\mathfrak{F}} \text{ such that } g R_{\mu}^{\mathfrak{F}} g' \tag{7.16}$$

$$\mathfrak{M}^{\mathfrak{F}}, \bullet, g \Vdash \exists x\phi \text{ iff } \mathfrak{M}^{\mathfrak{F}}, \bullet', g \Vdash \phi \text{ for some } \bullet' \text{ such that } \bullet' \sim_x \bullet \tag{7.17}$$

where $\bullet' \sim_x \bullet$ if $\bullet'(y) = \bullet(y)$ for all y such that $y \neq x$. That is, $\bullet$ and $\bullet'$ assign the same proteins to all variables but can differ with respect to the protein they assign to x. That a formula ϕ of $\mathcal{L}^{\mathcal{F}}$ is true in $\mathfrak{M}^{\mathfrak{F}}$ at gene $g \in G^{\mathfrak{F}}$ is written as $\mathfrak{M}^{\mathfrak{F}}, g \Vdash \phi$ and defined by the following semantic clause:

$$\mathfrak{M}^{\mathfrak{F}}, g \Vdash \phi \text{ iff } \mathfrak{M}^{\mathfrak{F}}, \bullet, g \Vdash \phi \text{ for all } \bullet \tag{7.18}$$

Predicate	Interpretation
$\mathit{Expressed}(t)$	t is expressed
$\mathit{Lethal}(t)$	t is lethal
$\mathit{SickleCell}(t)$	t causes sickle-cell disease
$\mathit{Known}(t)$	t is in HbVar
$\mathit{Fitter}(t, t')$	t is fitter than t'

Table 7.1
Predicates of the first-order protein language. Note that this list is by no means exhaustive.

With the first-order protein language in place, all kinds of observations can be expressed. For illustration, consider some possible predicates defined in Table 7.1. Two remarks are in order. First, $\mathit{Expressed}(t)$ serves a similar role as the predicate interpreted as actual existence which is usually found in languages describing constant domain models. The reason for wanting such a predicate is simple: Since the domain is the same for all genes and since the domain includes all proteins, all proteins exist at all genes. In order to distinguish random proteins from proteins expressed at a gene, $\mathit{Expressed}(t)$ is employed. There are of course some problems with this approach (see Garson 2014 for an overview), but they need not concern us here. Second, $\mathit{Fitter}(t, t')$ is somewhat awkward but reflects common usage, for example as witnessed by Weinreich et al. (2006). I take it that the other predicates are clear and will now discuss a number of observations that can be expressed with these sample predicates; for continuity, I will again focus on hemoglobin. To start off, consider the following sentences:

$$\mathfrak{M}^{\mathfrak{F}}, \mathit{HBB} \nVdash \exists x(\mathit{Expressed}(x) \wedge \mathit{SickleCell}(x)) \tag{7.19}$$

$$\mathfrak{M}^{\mathfrak{F}}, \mathit{HBB} \Vdash \langle M \rangle \exists x(\mathit{Expressed}(x) \wedge \mathit{SickleCell}(x)) \tag{7.20}$$

(7.19) states that it is false that *HBB* expresses a protein that causes sickle-cell disease; (7.19) is false since *HBB* expresses beta globin. By contrast, (7.20) states that at *HBB*, there is a single point mutation results in the expression of a protein that causes sickle-cell disease; (7.20) is true since HBB:c.20$\mathtt{A} \rightsquigarrow \mathtt{T}$ can be reached via a single substitution and expresses HbS that causes sickle-cell disease. Let me continue with something more

challenging (for sake of illustration, assume $n \geq 100$):

$$\mathfrak{M}^{\mathfrak{F}}, \mathit{HBB} \nVdash \forall x[M]^n(\mathit{Expressed}(x) \rightarrow \mathit{Lethal}(x)) \tag{7.21}$$

$$\mathfrak{M}^{\mathfrak{F}}, \mathit{HBB} \Vdash \forall x \, \Box^n_{\text{deletion}} \, (\mathit{Expressed}(x) \rightarrow \mathit{Lethal}(x)) \tag{7.22}$$

(7.21) states that it is false that at *HBB*, any sequence of n point mutations is such that it results in a gene where any protein is lethal if expressed; (7.21) is false since there is a sequence of n point mutations (namely substitutions) such that the resulting gene is type identical to *HBB* if n is even (otherwise the relevant resulting gene is HBB:c.21$\mathtt{G} \rightsquigarrow \mathtt{A}$ and hence qualitatively identical to *HBB* since the mutation is silent, as wanted). By contrast, (7.22) states that at *HBB*, any sequence of n single deletions is such that it results in a gene (in the technical sense of this section) where any protein is lethal if expressed. To clarify, a lethal deletion in this context is one that causes a severe form of beta thalassemia such as beta thalassemia major (see Galanello and Origa 2010 for an overview). Two qualifications are required which I will discuss in turn.

First, whether (7.22) holds is an empirical question that cannot be answered here. The reason is that the first-order generalized model contains many unknown HbA variants (that is, variants that are not recorded in HbVar). So while all known large deletions at *HBB* are (more or less) lethal, there might be exceptions that have not been observed yet. More generally, can a valuation in such cases be empirically adequate? If not, then the problem can perhaps be solved via a many-valued first-order modal logic that allows for indeterminate truth values whenever the valuation is not empirically adequate.[1] Note that this problem or limitation does not apply to the generalized model introduced in section 7.1 since the empirically adequate valuation can be constructed analytically.

Second, humans are heterozygous for *HBB* so there are two alleles or instances of *HBB* in somatic cells (one from each parent). Beta thalassemia major is an autosomal recessive disorder. That is, beta thalassemia major causally depends on both *HBB* alleles bearing thalassemia mutations. Put differently, by only considering one allele, it cannot be determined whether beta thalassemia major occurs. Therefore, the truth value of (7.22) cannot be determined. More generally, the generalized first-order model (and also the generalized model if additional propositional atoms are introduced) is in effect limited to homozygous genes. On a charitable reading of Dennett, we can assume that the Library of Mendel contains genomes with the appropriate zygosity; so this problem is specific to the generalized (first-order) model. There at least two possible solutions:

[1] I am not aware of any such logic but the starting point is Fitting (1991).

1. Replace the set of genes with the set of genomes with the required zygosity. While this is a simple fix, it reduces the tractability of the model.
2. Define the semantics of predicates that are sensitive to zygosity via a supervaluation. I have sketched such a solution for the generalized first-order model in appendix E..

Consider now a final sample sentence:

$$\mathfrak{M}^{\mathfrak{F}}, HBB \Vdash [M]^n \neg \exists x(Expressed(x) \wedge Known(x) \wedge Fitter(x, \mathrm{HbA})) \tag{7.23}$$

(7.23) states that no matter the sequence of point mutations, there is no known variant that is fitter than HbA.

7.2.2 Opaque versus transparent modalities

The $\Diamond_\mu \phi$ modality of the basic protein language respectively the $R^{\mathfrak{G}}_\mu$ relation of the generalized model is opaque. By this I mean that the position on the string at which a substitution, deletion or insertion occurs is neglected. As a consequence, it holds that:

$$\mathfrak{M}^{\mathfrak{G}} \nVdash \Diamond_{\mathrm{deletion}} \Diamond_{\mathrm{insertion}} \phi \rightarrow \Diamond_{\mathrm{substitution}} \phi \tag{7.24}$$

$$\mathfrak{M}^{\mathfrak{G}} \nVdash \Diamond_{\mathrm{insertion}} \Diamond_{\mathrm{deletion}} \phi \rightarrow \Diamond_{\mathrm{substitution}} \phi \tag{7.25}$$

Nevertheless, in some cases, a deletion followed by an insertion amounts to a substitution. If need be, this can be achieved via a what I call transparent $\Diamond_{\mu,n} \phi$ modality respectively $R^{\mathfrak{G}}_{\mu,n}$ relation where $n \in \mathbb{N}$ represents the position on the string at which μ occurs. The relevant semantic clause is:

$$\mathfrak{M}^{\mathfrak{G}}, g \Vdash \Diamond_{\mu,n} \phi \text{ iff } \mathfrak{M}^{\mathfrak{G}}, g' \Vdash \phi \text{ for some } g' \in G^{\mathfrak{G}} \text{ such that } g R^{\mathfrak{G}}_{\mu,n} g' \tag{7.26}$$

Then:

$$\mathfrak{M}^{\mathfrak{G}} \Vdash \Diamond_{\mathrm{deletion},n} \Diamond_{\mathrm{insertion},n} \phi \rightarrow \Diamond_{\mathrm{substitution},n} \phi \tag{7.27}$$

$$\mathfrak{M}^{\mathfrak{G}} \Vdash \Diamond_{\mathrm{insertion},n} \Diamond_{\mathrm{deletion},n} \phi \rightarrow \Diamond_{\mathrm{substitution},n} \phi \tag{7.28}$$

For example:

$$\mathfrak{M}^{\mathfrak{G}}, HBB \Vdash \Diamond_{\mathrm{deletion},20} \Diamond_{\mathrm{insertion},20} \mathrm{HbS} \rightarrow \Diamond_{\mathrm{substitution},20} \mathrm{HbS} \tag{7.29}$$

Note that the modalities of the basic amino acid language and the counting amino acid language (respectively the relation of the simple model) is opaque.

7.3 Summary

I show that the previously imposed modeling restrictions can be lifted via a generalization of the simple model. This enables the construction of logical models of any protein variant caused by any point mutation at the coding region of any gene. In the generalized model, states are interpreted as genes, multiple binary relations are interpreted as distinct point mutations, and the valuation is kept fixed and induces a partition of blocks of genes that code for some protein. I identify two limitations, namely (1) the limited expressive power and (2) the reliance on opaque modalities of the language describing the generalized model.

III. Applications

8. SMAC

SMAC (Simple Model Amino acid Checker) is a model checking tool implemented in Python and made publicly available at maxghuber.github.io/SMAC under the Apache License Version 2. It allows the user to obtain the truth value of any formula of the basic amino acid language $\mathcal{L}$ in the simple model $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ as defined in chapter 5, both locally and globally. In what follows, the main algorithm is briefly explained in section 8.1, the proof of its total correctness is given in section 8.2 and its computational complexity is discussed in section 8.3.

8.1 Algorithm

I begin with a high level description of the model checking algorithm. Two steps can be distinguished. First, the semantic structure of a formula ϕ given some codon of evaluation $c \in C$ is mapped to a tree in the following way: The root is decorated with ϕ and c. If ϕ is an atom, then the tree is finished. If not, ϕ is either a negation, a disjunction or a modal formula; if $\phi = \neg(\psi)$, then the root has one child which is decorated with ψ and c; if $\phi = \psi \vee \chi$, then the root has two children, one which is decorated with ψ and c, and one which is decorated with χ and c; if $\phi = \Diamond(\psi)$, then the root has nine children, each decorated with ψ and a unique codon that can be reached via single substitution from the codon of evaluation. This process is then applied recursively to the children of the root. The resulting tree is such that the semantic complexity of a formula at a node on a branch strictly decreases with the depth of the node (the leaf of every branch is an atom). Second, the tree is then evaluated as follows: If the root is an atom $p \in \Psi$, then ϕ is true if $c \in V(p)$. If not, ϕ is either a negation, a disjunction or a modal formula; if $\phi = \neg(\psi)$, then ϕ is true if its child is labeled false; if $\phi = \psi \vee \chi$ or $\phi = \Diamond(\psi)$ then ϕ is true if at least one of its children are labeled true. So in order to evaluate a branch, this process must be applied recursively until the leaf is evaluated.

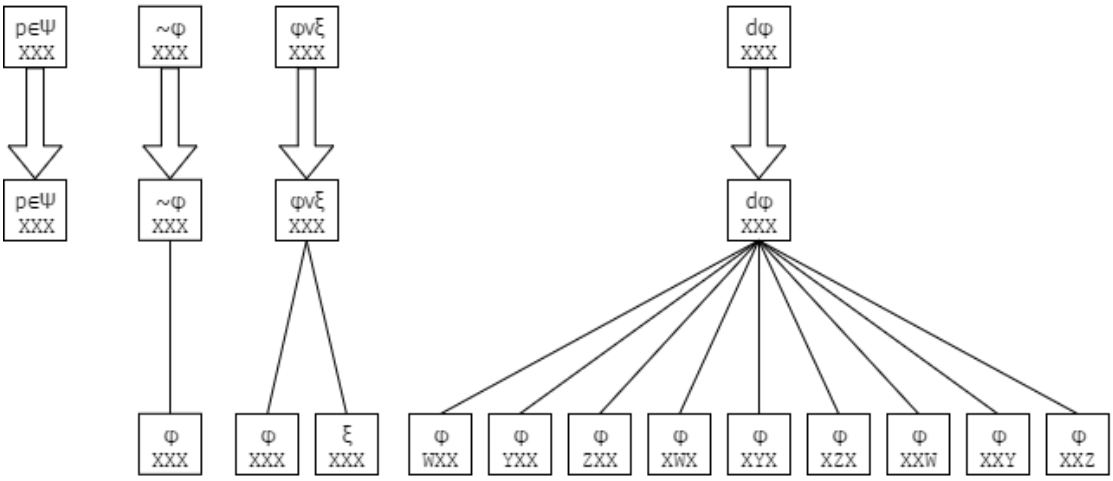


Figure 8.1
Visualization of the construction rules of `tree` for atoms, negation, disunction and diamond. Rectangles represent nodes and the big arrow represents (a single iteration of) `tree`. Note that the construction rules for disjunction and diamond are equivalent to the construction rules for conjunction and box (not depicted).

I now turn to a more formal description of the model checking algorithm. Consider first the definition of a node:

Definition 8.1 (Node)
A node N is a quadruple $\langle \phi, c, K, s \rangle$ such that:

- $\phi \in \mathcal{L}$ is a formula of the basic amino acid language,
- $c \in C$ is a codon,
- K is a n-tuple representing the children of N where $n \in \mathbb{N}_0$; by default, K is a 0-tuple,
- $s \in \{0, 1\}$ is the status of N, interpreted as 'unresolved' respectively 'resolved'; by default, s is unresolved.

For ease of presentation, I define two auxiliary functions:

- $h : \phi \to \{p \in \Psi, \neg, \vee, \wedge, \Diamond, \Box\}$ is a function that returns the the highest-ranking operator of ϕ. For example, $h(\mathsf{E})$ returns E, $h(\neg\mathsf{E})$ returns $\neg$, and $h(\mathsf{E} \vee \mathsf{Y})$ returns $\vee$.

- If $h(\phi)$ is unary, then $\phi = h(\phi)(\psi)$. Now $\phi/h(\phi)$ is a function that returns ψ. For example, $\neg\mathsf{E}/\neg = \mathsf{E}$. If $h(\phi)$ is binary, then $\phi = (\psi_1)h(\phi)(\psi_2)$; so $\phi/h_1(\phi)$ is a function that returns ψ_1 and $\phi/h_2(\phi)$ is a function that returns ψ_2. For example, $(\mathsf{E} \vee \mathsf{Y})/\vee_1 = \mathsf{E}$ and $(\mathsf{E} \vee \mathsf{Y})/\vee_2 = \mathsf{Y}$.

With these definitions at hand, a tree can be defined:

Definition 8.2 (Tree)

A tree T is the output of $\texttt{tree}(\mathfrak{M}, N)$ where $\mathfrak{M} = \langle C, R, \Phi, V\rangle$ and $N = \langle \phi, c, K, s\rangle$ such that:

```
def tree(𝔐, N):                                                    1
      if h(φ) == ¬:                                                2
            N′ = ⟨φ/h(φ), c, K′, s′⟩                               3
            K = ⟨N′⟩                                               4
      if (h(φ) == ∨ or h(φ) == ∧):                                 5
            N′ = ⟨φ/h1(φ), c, K′, s′⟩                              6
            N″ = ⟨φ/h2(φ), c, K″, s″⟩                              7
            K = ⟨N′, N″⟩                                           8
      if (h(φ) == ◇ or h(φ) == □):                                 9
            for substitution in {c′ : cRc′}                        10
                  N′ = ⟨φ/h(φ), substitution, K′, s′⟩              11
                  K = K.append(N′)                                 12
      for child in K:                                              13
            tree(𝔐,child)                                          14
      return N                                                     15
```

According to this definition, an update with `tree` transforms a node, interpreted as root, into a tree given the simple model; consider Figure 8.1 for a visualization of the corresponding construction rules. Note that all possible truth-makers are constructed. That is, if a node's formula is a disjunction, both disjuncts are constructed as children; and if a node's formula is a diamond, all codons that can be reached via single substitution from the node's codon are constructed as children. The resulting tree can then be checked in order to obtain the truth value of the root's formula given the root's codon:

Definition 8.3 (Local truth)

A formula ϕ is true at a codon $c \in C$ in the simple model $\mathfrak{M} = \langle C, R, \Phi, V\rangle$ if the value 'True' is returned by $\texttt{localtruth}(\mathfrak{M}, T)$ where $T = \langle \phi, c, K, s\rangle$ such that:

```
def localtruth(𝔐, T):                                                    1
      if h(ϕ) == p ∈ Ψ:                                                  2
            if c in V(ϕ):                                                3
                  ϕ = True                                               4
            else:                                                        5
                  ϕ = False                                              6
            s = resolved                                                 7
      if h(ϕ) == ¬:                                                      8
            for T′ in K:                                                 9
                  while s′ is not resolved:                              10
                        localtruth(𝔐, T′)                                11
                  if ϕ′ == True:                                         12
                        ϕ = False                                        13
                  else:                                                  14
                        ϕ = True                                         15
            s = resolved                                                 16
      if (h(ϕ) == ∨ or h(ϕ) == ◇):                                       17
            counter = 0                                                  18
            for T′ in K:                                                 19
                  while s′ is not resolved:                              20
                        localtruth(𝔐, T′)                                21
                  if ϕ′ == True:                                         22
                        counter += 1                                     23
                        break                                            24
            if counter > 0:                                              25
                  ϕ = True                                               26
            else:                                                        27
                  ϕ = False                                              28
            s = resolved                                                 29
      if (h(ϕ) == ∧ or h(ϕ) == □):                                       30
            counter = 0                                                  31
            for T′ in K:                                                 32
                  while s′ is not resolved:                              33
                        localtruth(𝔐, T′)                                34
                  if ϕ′ == True:                                         35
                        counter += 1                                     36
            if counter == |K|:                                           37
                  ϕ = True                                               38
            else:                                                        39
                  ϕ = False                                              40
            s = resolved                                                 41
      return ϕ                                                           42
```

Based on local truth, global truth is easily obtained:

Definition 8.4 (Global truth)
A formula ϕ is true the simple model $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ if for all $c \in C$ the value 'True' is returned by `localtruth`$(\mathfrak{M}, T)$ where $T = \langle \phi, c, K, s \rangle$.

Finally, note that SMAC can be extended in a straightforward manner to account for (most of) the graded models discussed in chapter 6 or the generalized model presented in chapter 7.

8.2 Total correctness

I now prove that total correctness holds of SMAC by proving that total correctness holds of `tree` and `localtruth`. For this, two conditions have to be satisfied assuming correct input data:

1. Stop property:
   (a) `tree` stops.
   (b) `localtruth` stops.
2. Partial correctness:
   (a) `tree` returns the correct output.
   (b) `localtruth` returns the correct output.

Lemma 8.1 (Stop property `tree`)
`tree` has the stop property.

Proof of lemma 8.1: Assume that $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ and $N = \langle \phi, c, K, s \rangle$ are correct. We show that `tree` has the stop property by showing that the recursive clause (see definition 8.2, lines 13–14) stops. (The loop at lines 10–12 stops trivially after nine iterations since there are exactly nine codons that can be reached via single substitution from any codon). By definition 5.2, every formula $\phi \in \mathcal{L}$ is built recursively from atoms. By assumption, ϕ is such a formula. Therefore, by only passing the formula(s) in the scope of the highest ranking operator of ϕ to the recursion (see definition 8.2, lines 3–4, 6–8,

11–12), it is guaranteed that, after finitely many steps, an atom is passed. Since nodes with atom labels do not have children, `tree` stops after finitely many steps. ■

Lemma 8.2 (Partial correctness `tree`)
Partial correctness holds of `tree`.

Proof of lemma 8.2: Assume that $\mathfrak{M} = \langle C, R, \Phi, V\rangle$ and $N = \langle \phi, c, K, s\rangle$ are correct. We show that partial correctness holds of `tree` by showing that if $\texttt{tree}(\mathfrak{M}, N)$ returns $T = \langle \phi, c, K, s\rangle$, then T represents all possible truth-makers of ϕ at c (call this property of T 'extended for ϕ at c'). We do so by induction on the complexity of ϕ. Assume that $\texttt{tree}(\mathfrak{M}, N)$ returns T:

Base: $\phi = p \in \Psi$.

1. By assumption, $\texttt{tree}(\mathfrak{M}, N)$ returns $T = \langle p, c, K, s\rangle$.
2. By 1 and the semantics of atoms (definition 5.2), T is extended for p at c.

Inductive hypothesis: Assume that partial correctness holds of `tree` for all ψ, χ that are less complex than ϕ: If $\texttt{tree}(\mathfrak{M}, \langle \psi, c, K, s\rangle)$ returns $T = \langle \psi, c, K, s\rangle$, then T is extended for ψ at c (and similar for χ).

Inductive step (five cases):

1. $\phi = \neg\psi$.
   i. By assumption, $\texttt{tree}(\mathfrak{M}, N)$ returns $T = \langle \neg\psi, c, K, s\rangle$.
   ii. By 1i. and the clause for negation (definition 8.2, lines 2–4), there is $N' \in K$ where $N' = \langle \psi, c, K', s'\rangle$.
   iii. By 1ii., the recursive clause (definition 8.2, lines 13–14) and lemma 8.1, $\texttt{tree}(\mathfrak{M}, N'$ returns $T' = \langle \psi, c, K', s'\rangle$.
   iv. By 1iii. and induction hypothesis, T' is extended for ψ at c.
   v. By 1iv. and the semantics for negation (definition 5.2), T is extended for $\neg\psi$ at c.
2. $\phi = \psi \vee \chi$.
   i. By assumption, $\texttt{tree}(\mathfrak{M}, N)$ returns $T = \langle \psi \vee \chi, c, K, s\rangle$.

ii. By 2i. and the clause for disjunction (definition 8.2, lines 5–8), there are $N', N'' \in K$ where $N' = \langle \psi, c, K', s' \rangle$ and $N'' = \langle \chi, c, K'', s'' \rangle$.

iii. By 2ii., the recursive clause (definition 8.2, lines 13–14) and lemma 8.1, $\texttt{tree}(\mathfrak{M}, N')$ returns $T' = \langle \psi, c, K', s' \rangle$ and $\texttt{tree}(\mathfrak{M}, N'')$ returns $T'' = \langle \chi, c, K'', s'' \rangle$.

iv. By 2iii. and induction hypothesis, T' is extended for ψ at c and T'' is extended for χ at c.

v. By 2iv. and the semantics for disjunction (definition 5.2), T is extended for $\psi \vee \chi$ at c.

3. $\phi = \Diamond\psi$.

i. By assumption, $\texttt{tree}(\mathfrak{M}, N)$ returns $T = \langle \Diamond\psi, c, K, s \rangle$.

ii. By 2i. and the clause for the $\Diamond$-modality (definition 8.2, lines 9–12), there are $N_1, \ldots, N_9 \in K$ such that $N_i = \langle \psi, c_i, K_i, s_i \rangle$ and cRc_i for $1 \leq i \leq 9$.

iii. By 3ii., the recursive clause (definition 8.2, lines 13–14) and lemma 8.1, $\texttt{tree}(\mathfrak{M}, N_i)$ returns $T_i = \langle \psi, c_i, K_i, s_i \rangle$.

iv. By 3iii. and induction hypothesis, T_i is extended for ψ at c_i.

v. By 3iv. and the semantics for the $\Diamond$-modality (definition 5.2), T is extended for $\Diamond\psi$ at c.

4. $\phi = \psi \wedge \chi$. Similar to 2.

5. $\phi = \Box\psi$. Similar to 3.

Therefore, T is extended for ϕ at c. ■

Lemma 8.3 (Stop property `localtruth`)
`localtruth` has the stop property.

Proof of lemma 8.3: Assume that $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ and $T = \langle \phi, c, K, s \rangle$ are correct. We show that `localtruth` has the stop property by showing that each recursive clause (see definition 8.3, lines 10–11, 20–21 and 33–34) stops. (The loops in which each of these clauses are embedded trivially stop after a maximum of nine iterations since there are maximally nine children per node, see Lemma 8.2). For any such clause, there are exactly two cases: s is resolved, or s is not resolved. In the first case, `localtruth` trivially

stops. In the second case, we need to show that all children $T' = \langle \phi', c', K', s' \rangle$ of T are such that s' is resolved. But since all leaves of the finite tree contained in T are atoms, s' must be resolved. (This can be made explicit by induction on the complexity of ϕ' which is skipped here.) Therefore, `localtruth` has the stop property. ■

Lemma 8.4 (Partial correctness `localtruth`)
Partial correctness holds of `localtruth`.

Proof of lemma 8.4: Assume that $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ and $T = \langle \phi, c, K, s \rangle$ are correct. We show that partial correctness holds of `localtruth` by showing that if `localtruth`$(\mathfrak{M}, T)$ returns the value 'True', then $\mathfrak{M}, c \Vdash \phi$. We do so by induction on the complexity of ϕ. Assume that `localtruth`$(\mathfrak{M}, T)$ returns the value 'True':

Base: $\phi = p \in \Psi$.

1. By assumption, `localtruth`$(\mathfrak{M}, \langle p, c, K, s \rangle)$ returns 'True'.
2. By 1. and the clause for atoms (definition 8.3, lines 2–7), $c \in V(p)$.
3. By 2. and semantics of atoms (definition 5.2), $\mathfrak{M}, c \Vdash p$.

Inductive hypothesis: Assume that partial correctness holds of `localtruth` for all ψ, χ that are less complex than ϕ: If `localtruth`$(\mathfrak{M}, \langle \psi, c, K, s \rangle)$ returns 'True', then $\mathfrak{M}, c \Vdash \psi$ (and similar for χ).

Inductive step (five cases):

1. $\phi = \neg\psi$.
   i. By assumption, `localtruth`$(\mathfrak{M}, \langle \neg\psi, c, K, s \rangle)$ returns 'True'.
   ii. By 1i and the clause for negation (definition 8.3, lines 8–16), there is a $\langle \psi, c', K', s' \rangle \in K$ such that `localtruth`$(\mathfrak{M}, \langle \psi, c', K', s' \rangle)$ returns 'False'.
   iii. By 1ii and induction hypothesis, not $\mathfrak{M}, c' \Vdash \psi$.
   iv. By lemma 8.2, $c' = c$.
   v. By 1iii and 1iv, not $\mathfrak{M}, c \Vdash \psi$.
   vi. By 1v and the semantics of negation (definition 5.2), $\mathfrak{M}, c \Vdash \neg\psi$.
2. $\phi = \psi \vee \chi$.

i. By assumption, `localtruth`$(\mathfrak{M}, \langle \psi \vee \chi, c, K, s \rangle)$ returns 'True'.

ii. By 2i. and the clause for disjunction (definition 8.3, lines 17–29), there is a $\langle \psi, c', K', s' \rangle \in K$ such that `localtruth`$(\mathfrak{M}, \langle \psi, c', K', s' \rangle)$ returns 'True' or there is a $\langle \chi, c'', K'', s'' \rangle \in K$ such that `localtruth`$(\mathfrak{M}, \langle \chi, c'', K'', s'' \rangle)$ returns 'True'.

iii. Assume that there is a $\langle \psi, c', K', s' \rangle \in K$ such that `localtruth`$(\mathfrak{M}, \langle \psi, c', K', s' \rangle)$ returns 'True'.

iv. By 2iii. and induction hypothesis, $\mathfrak{M}, c' \Vdash \psi$.

v. By lemma 8.2, $c' = c$.

vi. By 2iv. and 2v., $\mathfrak{M}, c \Vdash \psi$.

vii. By 2vi. and the semantics of disjunction (definition 5.2), $\mathfrak{M}, c \Vdash \psi \vee \chi$.

viii. Assume that there is a $\langle \chi, c'', K'', s'' \rangle \in K$ such that `localtruth`$(\mathfrak{M}, \langle \chi, c'', K'', s'' \rangle)$ returns 'True'.

ix. By 2viii. and similar to 2iv.–2vii, $\mathfrak{M}, c \Vdash \psi \vee \chi$.

x. By 2ii., 2vii. and 2ix., $\mathfrak{M}, c \Vdash \psi \vee \chi$.

3. $\phi = \Diamond\psi$.

i. By assumption, `localtruth`$(\mathfrak{M}, \langle \Diamond\psi, c, K, s \rangle)$ returns 'True'.

ii. By 3i. and the clause for the $\Diamond$-modality (definition 8.3, lines 17–29), there is a $\langle \psi, c', K', s' \rangle \in K$ such that `localtruth`$(\mathfrak{M}, \langle \psi, c', K', s' \rangle)$ returns 'True'.

iii. By 3ii. and induction hypothesis, $\mathfrak{M}, c' \Vdash \psi$.

iv. By lemma 8.2, cRc'.

v. By 3iii, 3iv. and the semantics of the $\Diamond$-modality (definition 5.2), $\mathfrak{M}, c \Vdash \Diamond\psi$.

4. $\phi = \psi \wedge \chi$. Similar to 2.

5. $\phi = \Box\psi$. Similar to 3.

Therefore, $\mathfrak{M}, c \Vdash \phi$. ∎

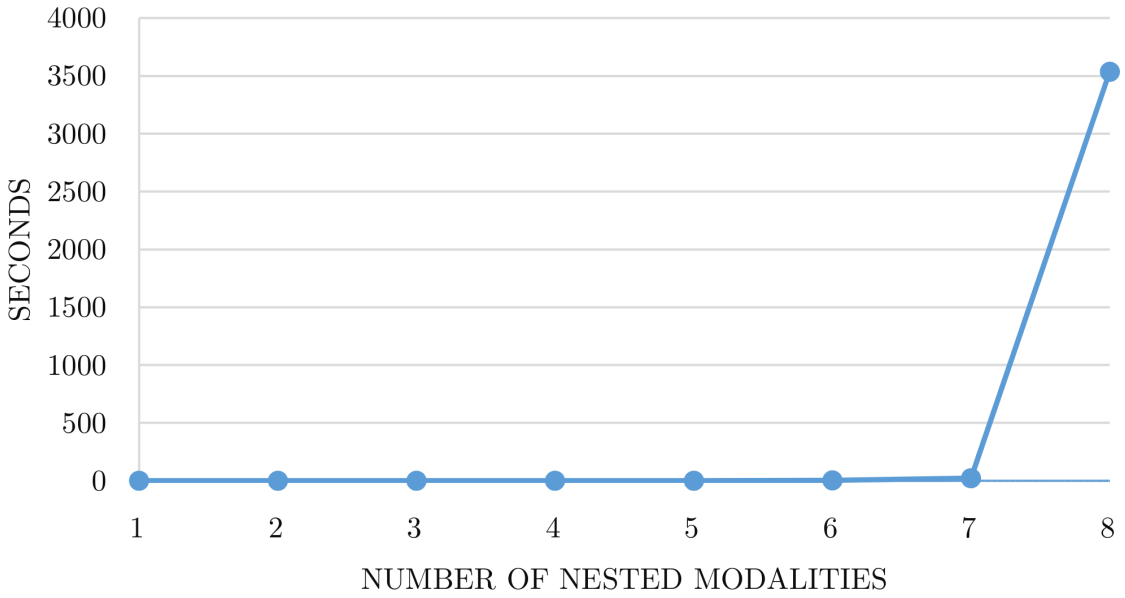


Figure 8.2
Diagram showing the exponential runtime of SMAC for nested modalities given an input formula $\Diamond^n \mathsf{E}$. The x-axis represents n, the y-axis indicates the running time as average over 10 trials in seconds. Note that this requires a 64 bit implementation of Python.

Theorem 8.1 (Total correctness SMAC)
Total correctness holds of SMAC.

Proof of theorem 8.1: Directly from lemmas 8.1–8.4. ∎

8.3 Computational complexity

SMAC does not scale well for largish inputs. More precisely, the running time of the composed `tree` and `localtruth` (see definitions 8.2 and 8.3) is determined by the input formula ϕ: If ϕ contains nested modal operators, then the algorithm scales exponentially where the exponent is given by the (highest) number n of nested modal operators ($\mathcal{O}(2^n)$ in Landau notation).

The main reason for this bad performance is that SMAC represents formulas as trees. Representing formulas as trees is intuitive since the logically possible truth-makers of a

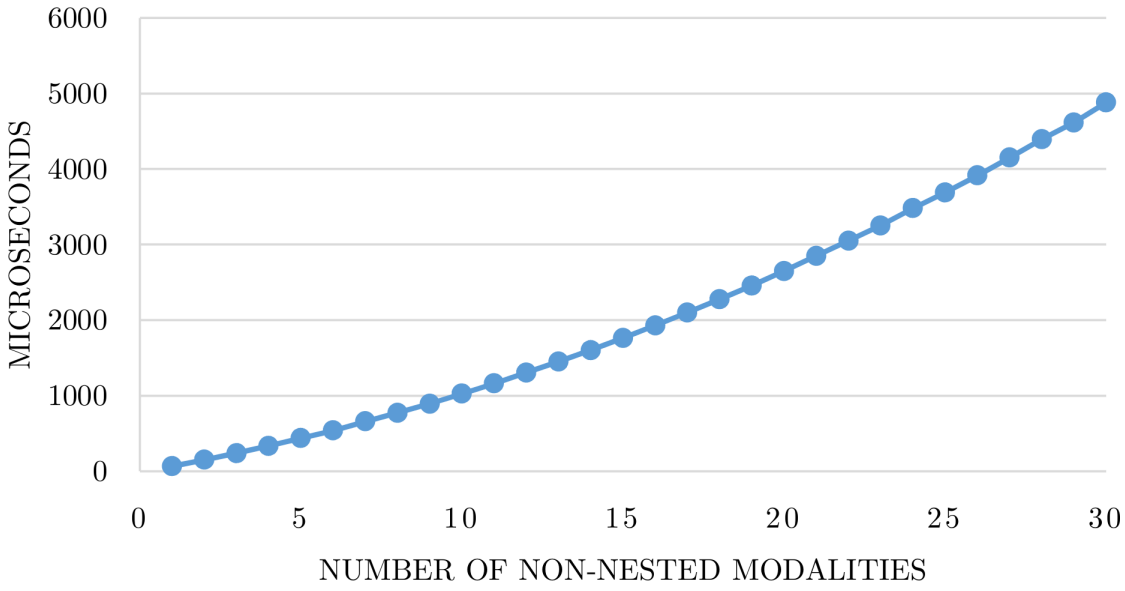


Figure 8.3
Diagram showing the polynomial runtime of SMAC for non-nested modalities given an input formula $\Diamond_1 \mathsf{E} \wedge \cdots \wedge \Diamond_n \mathsf{E}$. The x-axis represents n, the y-axis indicates the running time as average over 10000 trials in microseconds.

modal operator are represented as the children of a node. However, it is also costly. To see this, consider a formula with nested modalities such as $\Diamond^n \mathsf{E}$. Neglecting detail, the required tree has at least 9^n branches; so for $n = 10$, there are approximately 3.5 billion branches. The pragmatic cutoff is at $n = 7$ as illustrated in Figure 8.2. Note that if the formula only contains non-nested modal operators, then the algorithm is solvable in polynomial time. See Figure 8.3 for an example.

The algorithm can be optimized. For example, instead of first constructing all branches of the tree and evaluating in a second step, branches could be constructed and evaluated sequentially. To see this, take a node with $\Diamond\phi$ (and similar for $\phi \vee \psi$). Here only one child where ϕ holds must be constructed. The inverse holds for $\Box\phi$ (and $\phi \wedge \psi$). Here only one child where ϕ does not hold must be constructed. Which child to construct first could be determined randomly; or, perhaps more promising, based on context-dependent probabilities. However, let me underscore that these optimizations do not exclude the worst case where all truth-makers (respectively the tree in full) have to be constructed. A more efficient algorithm that might be applied to the simple model is for example discussed by Shirazi and Amir (2008).

8.4 Summary

I present SMAC (Simple Model Amino acid Checker), a model checking tool implemented in Python and made publicly available at maxghuber.github.io/SMAC under the Apache License. It allows the user to obtain the truth value of any formula ϕ of the basic amino acid language in the simple model. SMAC builds a semantic tree where the root is the codon of evaluation decorated with ϕ, descendants are codons decorated with subformulas of ϕ, and the leafs jointly comprise all logically possible truth makers of ϕ. Each branch is then evaluated bottom-up. I show that SMAC has the total correctness property, and that SMAC scales exponentially for nested modal operators where the exponent is given by the highest number of nested modal operators.

9. Biological counterfactuals

In section 9.1, I will present David Lewis' (1973) semantics of counterfactual conditionals (LSC in short) both informally and formally. In section 9.1, after briefly reviewing the standard worries, I will make explicit a number of problems specific to applying LSC to biological counterfactuals.[1] Finally, in section 9.3, I will provide a new semantics of biological counterfactuals based on the results of part II.

9.1 Lewis' semantics of counterfactual conditionals

In this section, I will informally introduce LSC and then provide a formalization in the spirit of the models in part II. Both the informal and the formal part are based on my Leahy and Huber (2014).

Lewis' semantics employs possible worlds and similarity among possible worlds as basic notions in providing a semantics for counterfactuals such as:

If Bill had come to the party, it would have been fun. (9.1)

In order to check whether a counterfactual such as (9.1) is true in the actual world, one goes to the possible world that is maximally similar to the actual world and where the antecedent is true (that is, the world as it would have been if Bill had come to the party) and checks whether or not the party was fun there. If it was, then the counterfactual is true; if it was not, then the counterfactual is false. In the following, @ will be used to denote the actual world.

However, two complications are required. First, it may not be that there is a single maximally similar world to @ where the antecedent is true. Consider: Bill did not come

[1] I do not distinguish between 'biological counterfactuals' and 'biological counterfactual conditionals'.

to the party, but if he had, would he have arrived at 19:45 or at 20:00? There may be a world w where Bill arrived at 19:45 and a distinct world w' where Bill arrived at 20:00, where both w and w' are equally good candidates for being the most similar world to @ where Bill came. That is, non-identical worlds may be tied for similarity. So we need to complicate the truth conditions for counterfactuals. In order to check whether a counterfactual conditional such as $\phi \rightsquigarrow \psi$ is true in @, find the set of possible worlds that are maximally similar to @ and where the antecedent ϕ is true and check whether the consequent ψ is true at all those worlds. If it is, then the counterfactual is true; if it is not, then the counterfactual is false. The members of the set of maximally similar antecedent worlds are called 'evaluation worlds' for any conditional with that antecedent.

Second, for some sentence ϕ, there may not be a maximally similar world to @ where ϕ is true. This can happen in two ways:

1. There are no ϕ-worlds. For Lewis, any counterfactual with such an antecedent is vacuously true.

2. There is an infinite sequence of ϕ-worlds, each more similar to @ than the last. In this case we cannot speak of the (set of) maximally similar world(s) to @. For example, Jim is 180 cm tall. Are there worlds maximally similar to @ where Jim is over 180 cm tall? How tall is he in those worlds? If he is 180.5 cm in w, it seems that w', where he is 180.25 cm, is more similar to @ (since Jim's height in w' is closer to his height in @ than is his height in w). But then consider w'', where Jim is 180.125 cm. World w'' is more similar to @ than is w'. We can continue this sequence infinitely, and never get to a maximally similar ϕ-world.

This latter possibility complicates Lewis' truth conditions for counterfactuals substantially, but need not bother us for the purposes of this chapter. None of the antecedents we will consider are ones for which there is an infinite sequence of possible worlds, each more similar to @ than the last, where the antecedent is true. So for each antecedent ϕ we consider we may safely refer to the set of maximally similar ϕ-worlds to @. Therefore, a counterfactual $\phi \rightsquigarrow \psi$ is true just in case the maximally similar ϕ-worlds are all ψ-worlds.

I now turn to formalize LSC. I will begin by defining a Lewis model:

Definition 9.1 (Lewis model)
A Lewis model $\mathfrak{L}$ is a quadruple $\left\langle W^{\mathfrak{L}}, \leq^{\mathfrak{L}}, \Phi^{\mathfrak{L}}, V^{\mathfrak{L}} \right\rangle$ such that:

- $W^{\mathfrak{L}}$ is a non-empty set interpreted as the set of possible worlds. In addition, stipulate that $@ \in W^{\mathfrak{L}}$.
- $\leq^{\mathfrak{L}}$ is a total preorder (i.e., a transitive and total binary relation) on $W^{\mathfrak{L}}_{@} \subseteq W^{\mathfrak{L}}$ where $W^{\mathfrak{L}}_{@}$ is interpreted as the set of possible worlds that are accessible from $@$. $\leq^{\mathfrak{L}}$ is interpreted as comparative similarity relation with respect to $@$.
- $\Phi^{\mathfrak{L}}$ is the set of atomic propositions.
- $V^{\mathfrak{L}} : \Phi^{\mathfrak{L}} \to \mathcal{P}(W^{\mathfrak{L}})$ is a valuation function which assigns to each atomic proposition $p \in \Phi^{\mathfrak{L}}$ some set of worlds $V^{\mathfrak{L}}(p) \subseteq W^{\mathfrak{L}}$. Intuitively, $V^{\mathfrak{L}}(p)$ is interpreted as the set of worlds $w \in W^{\mathfrak{L}}$ where p is true.

For $w, w' \in W^{\mathfrak{L}}_{@}$, $w \leq^{\mathfrak{L}} w'$ expresses that w is at least as similar to $@$ as w'. For simplicity, let $w <^{\mathfrak{L}} w'$ abbreviate that it is not the case that $w' \leq^{\mathfrak{L}} w$; so $w <^{\mathfrak{L}} w'$ expresses that w is more similar to $@$ than w'. The similarity relation will be discussed alongside the accessibility relation in more detail in the next section.

The Lewis language is the language of propositional logic with the addition of the binary '$\rightsquigarrow$'-operator for counterfactual conditionals:

Definition 9.2 (Lewis language)
The Lewis language $\mathcal{L}^{\mathcal{L}}$ is used to describe Lewis models $\mathfrak{M}^{\mathfrak{L}} = \left\langle W^{\mathfrak{L}}, \leq^{\mathfrak{L}}, \Phi^{\mathfrak{L}}, V^{\mathfrak{L}} \right\rangle$. The syntax of $\mathcal{L}^{\mathcal{L}}$ is given by the following Backus-Naur form:

$$\phi \;:=\; p \mid \neg\phi \mid \phi \vee \phi \mid \phi \rightsquigarrow \phi$$

where $p \in \Phi^{\mathcal{L}}$. The standard abbreviations for the classical connectives $\wedge, \rightarrow, \leftrightarrow$ are used. That a formula ϕ of $\mathcal{L}^{\mathcal{L}}$ is true in $\mathfrak{M}^{\mathfrak{L}}$ at a world $w \in W^{\mathfrak{L}}$ is written as $\mathfrak{M}^{\mathfrak{L}}, w \Vdash \phi$. The semantics of $\mathcal{L}^{\mathcal{L}}$ are given recursively:

$$\mathfrak{M}^{\mathfrak{L}}, w \Vdash p \text{ iff } w \in V^{\mathfrak{L}}(p) \tag{9.2}$$

$$\mathfrak{M}^{\mathfrak{L}}, w \Vdash \neg\phi \text{ iff not } \mathfrak{M}^{\mathfrak{L}}, w \Vdash \phi \tag{9.3}$$

$$\mathfrak{M}^{\mathfrak{L}}, w \Vdash \phi \vee \psi \text{ iff } \mathfrak{M}^{\mathfrak{L}}, w \Vdash \phi \text{ or } \mathfrak{M}^{\mathfrak{L}}, w \Vdash \phi \tag{9.4}$$

$$\mathfrak{M}^{\mathfrak{L}}, @ \Vdash \phi \rightsquigarrow \psi \text{ iff} \tag{9.5}$$
$$\forall w \in W^{\mathfrak{L}}_{@} \text{ s.t. } \mathfrak{M}^{\mathfrak{L}}, w \Vdash \phi : \exists w' \in W^{\mathfrak{L}}_{@} \text{ s.t. } \mathfrak{M}^{\mathfrak{L}}, w' \Vdash \phi \text{ and } w' \leq^{\mathfrak{L}} w, \text{ and}$$
$$\forall w'' \in W^{\mathfrak{L}}_{@} \text{ such that } \mathfrak{M}^{\mathfrak{L}}, w'' \Vdash \phi \text{ and } w'' \leq^{\mathfrak{L}} w' : \mathfrak{M}^{\mathfrak{L}}, w'' \Vdash \psi$$

A counterfactual conditional such as $\phi \rightsquigarrow \psi$ expresses that if ϕ had been the case, ψ would be the case. Given the basic Lewis language, the semantics of counterfactual conditionals are quite involved as witnessed by (9.5). Fortunately, (9.5) can be simplified by requiring Lewis models $\mathfrak{M}^{\mathfrak{L}}$ to be limited (see Lewis 1973: 19f.):

Definition 9.3 (Limited Lewis model)
A Lewis model $\mathfrak{M}^{\mathfrak{L}} = \left\langle W^{\mathfrak{L}}, \leq^{\mathfrak{L}}, \Phi^{\mathfrak{L}}, V^{\mathfrak{L}} \right\rangle$ is limited if and only if $\leq^{\mathfrak{L}}$ is well-founded.

If a Lewis model $\mathfrak{M}^{\mathfrak{L}}$ is limited, then the set of accessible worlds $W^{\mathfrak{L}}_{@} \subseteq W^{\mathfrak{L}}$ has at least one world $w \in W^{\mathfrak{L}}_{@}$ which is maximally similar to @. In other words, infinite chains of ever more similar possible worlds in $W^{\mathfrak{L}}_{@}$ are excluded. For any limited Lewis model $\mathfrak{M}^{\mathfrak{L}}$, let $M^{\mathfrak{L}}_{@} \subseteq W^{\mathfrak{L}}_{@}$ be the set of maximally similar possible worlds with respect to @:

$$w \in M^{\mathfrak{L}}_{@} \text{ if and only if } \neg\exists w' \in W^{\mathfrak{L}}_{@} \text{ such that } w' <^{\mathfrak{L}} w \tag{9.6}$$

By the same token, if there is an ϕ-world, then there is a nonempty set of maximally similar possible ϕ-worlds $M^{\mathfrak{L}}_{@/\phi} \subseteq W^{\mathfrak{L}}_{@}$ with respect to @:

$$w \in M^{\phi}_{@/\phi} \text{ if and only if } \mathfrak{M}^{\mathfrak{L}}, w \Vdash \phi \text{ and } \neg\exists w' \in W^{\mathfrak{L}}_{@} \text{ such that } w' <^{\mathfrak{L}} w \text{ and } \mathfrak{M}^{\mathfrak{L}}, w' \Vdash \phi \tag{9.7}$$

For the class of limited Lewis models, the semantic clause for counterfactual conditionals (9.5) can hence be replaced by the more simple (see Lewis 1973: 19f.):

$$\mathfrak{M}^{\mathfrak{L}}, @ \Vdash \phi \rightsquigarrow \psi \text{ iff } \forall w \in M^{\mathfrak{L}}_{@/\phi} : \mathfrak{M}^{\mathfrak{L}}, w \Vdash \psi \tag{9.8}$$

That is, a counterfactual conditional $\phi \rightsquigarrow \psi$ is true at the actual world in a Lewis model if and only if all maximally similar (and accessible) ϕ-worlds are also ψ-worlds. With the Lewis language in place, note that the provided semantics are not general. To see this, consider that the semantic clauses for counterfactual conditionals (9.5) and (9.8) are only defined with respect to the actual world. That is, I have simplified the semantics by defining the comparative similarity ordering only relative to the actual world. A general

semantics would define an accessibility relation and a comparative similarity ordering for every possible world in any Lewis model. In other words, the presented model is a pointed model and the Lewis language is used to describe such pointed models. However, these simplifications are adopted because they ease presentation without harm to my purposes as I am not not concerned with any embedded counterfactual conditionals here. This completes formalizing LCS.

9.2 Problems

There are number of problems with LCS that have been discussed in detail elsewhere (e.g., Schulz 2011). However, in this section, I am concerned exclusively with problems that stem from applying LSC to biological counterfactuals.

The main problem with LCS is the comparative similarity relation. To see this, recall first the definition of a Lewis model: In order to construct a Lewis model, a similarity ordering needs to be induced on the set of accessible worlds. But how can we tell whether or not world w is more similar to the actual world than world w'? Lewis' (1979) approach is to consider what violations of natural law are required to transform the actual world into w respectively w'; he calls such violations 'miracles'.[2] Assuming that neither of w, w' is numerically identical to the actual world, Lewis proposes that w is more similar to the actual world than w' if and only if the miracle required to transform the actual world into w is smaller than the miracle required to transform the actual world into w'. Lewis offers a "system of weights or priorities" (1979: 472) to get a grip on the size (for lack of a better term) of a miracle. In what follows, I will refer to this system as 'minimal violation principle' (MVP in short, verbatim from Lewis 1979: 472):

1. It is of the first importance to avoid big, widespread, diverse violations of law.
2. It is of the second importance to maximize the spatio-temporal region throughout which perfect match of particular fact prevails.
3. It is of the third importance to avoid even small, localized, simple violations of law.
4. It is of little or no importance to secure approximate similarity of particular fact, even in matters that concern us greatly.

[2] This approach was intended to supplement LCS after having been charged of being too vague with respect to the comparative similarity relation, for example by Kit Fine (1975).

So MVP is used to determine an ordering of worlds in terms of miracles which is interpreted in turn as ordering of worlds in terms of similarity as required by definition 9.1. There are a number of general issues with MVP: Are the clauses in the right order? Are there clauses missing? And so on. However, as mentioned above, these general issues do not concern us here. Rather, I want to make the case that MVP spells trouble for applying LCS to biological counterfactuals. Here are the two reasons to support my claim:

First, assume that MVP as given is correct. In order to tackle specific biological counterfactuals such as presented in section 1.2, we need to be able to provide a similarity ordering in practice. That is, a concrete Lewis model needs to be constructed. However, this is an unfeasible task since worlds are too big and there are too many worlds. What is more, even if we had the (computational) resources to build a Lewis model, an ordering of worlds based on MVP is in many cases not epistemically available. Second, assume that these pragmatic and epistemic concerns with respect to MVP can be overcome. Since similarity is cashed out in terms of physical laws but not all biological explanations are reducible to explanations in terms of physical laws, there is an explanatory mismatch. In order to better understand the notion of an explanatory mismatch, consider the following two examples:

1. Small physical change, big biological change. Take codon `GAG` which codes for glutamine and consider two of its variants, namely `GAA` which also codes for glutamine and `TAG` which terminates translation. According to MVP, `GAA` and `TAG` are equisimilar to `GAG` since the same type of miracle is required to transform `GAG` into `GAA` and `TAG` respectively. However, from a biological perspective, the former is a silent mutation whereas the latter is a nonsense mutation. In other words, a glutamine-world is more similar to glutamine-world than to a termination-world.

2. Large physical change, small biological change. Take codon `TCA` which codes fo serine and consider two of its variants, namely `AGC` which also codes for serine and `TAA` which terminates translation. According to MVP, `TAA` is more similar to `TCA` than `AGC` since the miracle required to transform `TCA` into `AGC` is bigger than the miracle required to transform `TCA` into `TAA`.[3] However, from a biological perspective, the former is a silent mutation whereas the latter is a nonsense mutation. In other words, a serine-world is more similar to serine-world than to a termination-world.

[3] Whatever the exact arithmetic of miracles is, assume that the transformation from `TCA` into `TAA` requires one miracle. Then the transformation from `TCA` into `AGC` requires three miracles of this type.

There are two objections to this argument. I discuss them briefly with respect to the first example. It could be argued that `GAA` and `TAG` are not equisimilar to `GAG` since the required substitutions occur at different rates. For this objection to get off the ground, the assumed rates must be (deducible from) a physical law (and not just "particular fact[s]" Lewis 1979: 472). Furthermore, assuming there are probabilistic laws, why should a transformation into an unlikely event be a bigger violation of such a law than a transformation into another, more likely event? In any case, it is easy to find analogous examples where the required substitutions occur at identical rates. Second, it could be argued that `GAA` and `TAG` are not equisimilar to `GAG` since `GAA` is a glutamine-world whereas `TAG` is not. However, this objection misses the point: On the reductionist view (be it ontological or explanatory), there is nothing more to the difference between the glutamine-world and the termination-world than their respective physical basis; and the miracles to bring about each world are type identical.

To recapitulate, the main problem with LCS is its inadequacy with respect to biological counterfactuals which stems from basing the comparative similarity relation on MVP. Two remarks are in order: First, the discussed problem does not touch the correctness of the semantics of counterfactual conditionals as stated in (9.5) and (9.8) since the Lewis language is used to describe an already constructed Lewis models. The problem is more basic: If it is not feasible to construct Lewis models for pragmatic and epistemic reasons, then the provided semantics of counterfactual conditionals are utterly useless. Second, the problem is not limited to biology but carries over to other special sciences.

There are three strategies in response to the inadequacy of LCS. The first strategy is to tweak MVP by adding clauses for special science laws. This strategy is employed by Jeff Dunn (2011) and by Daniel Dohrn and Thomas Kroedel (2013). While I remain agnostic about this strategy with respect to the special sciences general, I submit that it is a non-starter for biology based on the arguments presented in section 2.1, namely the contentious hierarchy of the clauses (relation between physical and biological laws), the circularity worry, and the question of whether there actually are biological laws. The second strategy is give up on providing semantics for biological counterfactuals. For example, Marco Nathan (forthcoming) argues that one should rather focus on the pragmatic role that counterfactuals play in predictions and explanations. Finally, a third strategy is to amend LCS by replacing MVP with a more adequate principle. In other words, the third strategy is to induce the similarity ordering via a principle different than MVP. In the next section, I will explore an implementation of this strategy.

9.3 Semantics for biological counterfactuals

In this section, I will provide a semantics for biological counterfactuals that avoids the problems encountered with LCS. The most important move is to replace the Lewis model with a model more adequate to biology. The resulting semantics for counterfactual conditionals remain true to the spirit of LCS.

I begin by defining an adequate Lewis model (adequate, to be sure, for the application to biological counterfactuals):

Definition 9.4 (Adequate Lewis model)
An adequate Lewis model $\mathfrak{M}^{\mathfrak{A}}$ is a quadruple $\left\langle C^{\mathfrak{A}}, \leq_c^{\mathfrak{A}}, \Phi^{\mathfrak{A}}, V^{\mathfrak{A}} \right\rangle$ such that:

- $C^{\mathfrak{A}}$ is the set of codons C as per definition 5.1.
- For each $c \in C^{\mathfrak{A}}$, $\leq_c^{\mathfrak{A}}$ is a total preorder on $C^{\mathfrak{A}}$ and interpreted comparative similarity relation with respect to c.
- $\Phi^{\mathfrak{A}}$ is the set of atomic propositions Φ as per definition 5.1.
- $V^{\mathfrak{A}} : \Phi^{\mathfrak{A}} \to \mathcal{P}(C^{\mathfrak{A}})$ is the valuation V as per definition 5.1.

An adequate Lewis model is hence a simple model as per definition 5.1 where the single substitution relation has been replaced with a comparative similarity relation.

Three remarks about this relation are in order. First, for $c, c', c'' \in C^{\mathfrak{A}}$, $c' \leq_c^{\mathfrak{A}} c''$ expresses that c' is at least as similar to c as c''. For simplicity, let $c' <_c^{\mathfrak{A}} c''$ abbreviate that it is not the case that $c'' \leq_c^{\mathfrak{A}} c'$; so $c' <_c^{\mathfrak{A}} c''$ expresses that c' is more similar to c than c''. My second remark concerns the way in which the similarity ordering is induced. In contrast to the similarity ordering of LCS which is between worlds and induced by the non-violation principle, the similarity ordering in the adequate Lewis model is induced by comparing edit distances between codons (recall definition 3.26):

$$c' \leq_c^{\mathfrak{A}} c'' \text{ iff } \delta(c, c') \leq \delta(c, c'') \tag{9.9}$$

That is, c' is at least as similar to c as c'' if and only if the edit distance from c to c' is equal or smaller as compared to the edit distance from c to c''. Note that this is rather a schema of how the similarity ordering is induced since there are many different implementations of edit distance. For example, all of the grades of biological possibility respectively their

model basis discussed in chapter 6 qualify. Finally, for ease of presentation, in what follows I will assume that the comparative similarity relation is well-founded (that is, that the adequate Lewis model is limited).

There are three main advantages of the adequate Lewis model $\mathfrak{M}^{\mathfrak{A}}$ over the Lewis model $\mathfrak{M}^{\mathfrak{L}}$ with respect to biological counterfactuals:

1. In light of section 2.1 where I have identified the problems of defining biological modalities in terms of biological laws, the most important advantage of $\mathfrak{M}^{\mathfrak{A}}$ over $\mathfrak{M}^{\mathfrak{L}}$ is that in contrast to the latter, the former does not rely on physical or biological laws. More precisely, the similarity ordering in $\mathfrak{M}^{\mathfrak{L}}$ is stated in terms of minimizing the violation of physical and/or biological laws. By contrast, the similarity ordering in $\mathfrak{M}^{\mathfrak{L}}$ does neither invoke physical nor biological laws.

2. $\mathfrak{M}^{\mathfrak{A}}$ is less metaphysically and/or epistemically loaded than $\mathfrak{M}^{\mathfrak{L}}$. Whatever possible worlds are, codons are simpler objects. One does not have to be a modal realist to appreciate this point; even on formalist accounts of possible world, codons can be represented as smaller sets of propositions. More importantly, $\mathfrak{M}^{\mathfrak{A}}$ does not require an accessibility relation on top of the comparative similarity relation. This point needs a twofold qualification: Below I argue, first, that $\mathfrak{M}^{\mathfrak{A}}$ can be merged with $\mathfrak{M}$, and, second, that $\mathfrak{M}^{\mathfrak{A}}$ can be generalized analogously to the method presented in chapter 7. In both cases, an accessibility relation will be required. The advantage of my account is that the accessibility relation is well-defined in terms of edit distance and not based on the vague and intuition fueled idea of conceivability.

3. This is related to the first advantage, but worth stating explicitly: The comparative similarity relation in $\mathfrak{M}^{\mathfrak{A}}$ is well-defined for many implementations of edit distance whereas the comparative similarity relation in $\mathfrak{M}^{\mathfrak{L}}$ is not well-defined. What is more, the comparative similarity relation in $\mathfrak{M}^{\mathfrak{A}}$ is decidable given interesting implementations of edit distance such as Hamming distance.

I will now turn to defining the adequate Lewis language:

Definition 9.5 (Adequate Lewis language)
Adequate models $\mathfrak{M}^{\mathfrak{A}} = \left\langle C^{\mathfrak{A}}, \leq_c^{\mathfrak{A}}, \Phi^{\mathfrak{A}}, V^{\mathfrak{A}} \right\rangle$ are described by the adequate Lewis language $\mathcal{L}^{\mathcal{A}}$. The syntax of $\mathcal{L}^{\mathcal{A}}$ is given by the following Backus-Naur form:

$$\phi \;:=\; p \mid \neg\phi \mid \phi \vee \phi \mid \phi \rightsquigarrow \phi$$

where $p \in \Phi^{\mathcal{A}}$. The standard abbreviations for the classical connectives $\wedge, \rightarrow, \leftrightarrow$ are used. That a formula ϕ of $\mathcal{L}^{\mathcal{A}}$ is true in $\mathfrak{M}^{\mathfrak{A}}$ at a codon $c \in C^{\mathfrak{A}}$ is written as $\mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi$. The semantics of $\mathcal{L}^{\mathcal{A}}$ are given recursively:

$$\mathfrak{M}^{\mathfrak{A}}, c \Vdash p \text{ iff } c \in V^{\mathfrak{A}}(p) \tag{9.10}$$

$$\mathfrak{M}^{\mathfrak{A}}, c \Vdash \neg\phi \text{ iff not } \mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi \tag{9.11}$$

$$\mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi \vee \psi \text{ iff } \mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi \text{ or } \mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi \tag{9.12}$$

$$\mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi \rightsquigarrow \psi \text{ iff } \forall c' \in M^{\mathfrak{A}}_{c/\phi} : \mathfrak{M}^{\mathfrak{A}}, c' \Vdash \psi \tag{9.13}$$

where $M^{\mathfrak{A}}_{c/\phi} \subseteq C^{\mathfrak{A}}$ is the set of maximally similar ϕ-codons with respect to c:

$$c' \in M^{\mathfrak{A}}_{c/\phi} \text{ iff } \mathfrak{M}^{\mathfrak{A}}, c' \Vdash \phi \text{ and } \neg\exists c'' \in C^{\mathfrak{A}} \text{ such that } c'' <^{\mathfrak{A}}_{c} c' \text{ and } \mathfrak{M}^{\mathfrak{A}}, c'' \Vdash \phi \tag{9.14}$$

Note that the adequate Lewis model can be generalized analogously to the simple model as discussed in chapter 7.

9.4 Total models and languages

An additional advantage of the presented semantics of biological counterfactuals is that they integrate seamlessly with the semantics of biological possibility presented in part II. More precisely, we can combine any model presented in part II with the adequate Lewis model; these models in turn can be described a combination of an amino acid language and the adequate Lewis language.[4] For future reference, call the result of combining a model x with the adequate Lewis model a total model x, and call the result of combining an amino acid language y with the adequate Lewis language a total language y. A total model and corresponding total language therefore provide an integrated semantics for biological possibility, necessity and counterfactuality of a certain grade. This satisfies desideratum (D6) stated in subsection 1.3.1 of giving a unified treatment of these modalities.

Let me now make the idea of combining models respectively languages more precise. For illustration, consider combining the simple model $\mathfrak{M}$ with the adequate Lewis model $\mathfrak{M}$, and combining the basic amino acid language $\mathcal{L}$ with the adequate Lewis language $\mathcal{L}^{\mathcal{A}}$. I begin by defining the former:

[4] This does not hold for the probabilistic model and language, or is at least not as straightforward.

Definition 9.6 (Total simple model)
A total simple model $\mathfrak{M}^{\mathfrak{T}}$ is a quintuple $\left\langle C^{\mathfrak{T}}, R^{\mathfrak{T}}, \leq_c^{\mathfrak{T}}, \Phi^{\mathfrak{T}}, V^{\mathfrak{T}} \right\rangle$ such that:

- $C^{\mathfrak{T}}$ is the set of codons C as per definition 5.1.
- $R^{\mathfrak{T}} \subseteq C^{\mathfrak{T}} \times C^{\mathfrak{T}}$ is a symmetric binary relation interpreted as single substitution as per definition 5.1.
- For each $c \in C$, $\leq_c^{\mathfrak{T}}$ is a total preorder on $C^{\mathfrak{T}}$ interpreted as comparative similarity relation with respect to c as per definition 9.4.
- $\Phi^{\mathfrak{A}}$ is the set of atomic propositions Φ as per definition 5.1.
- $V^{\mathfrak{A}} : \Phi^{\mathfrak{A}} \to \mathcal{P}(C^{\mathfrak{A}})$ is the valuation V as per definition 5.1.

Let me now turn to the definition of the total basic amino acid language:

Definition 9.7 (Total basic amino acid language)
Total simple models $\left\langle C^{\mathfrak{T}}, R^{\mathfrak{T}}, \leq_c^{\mathfrak{T}}, \Phi^{\mathfrak{T}}, V^{\mathfrak{T}} \right\rangle$ are described by the total basic amino acid language $\mathcal{L}^{\mathcal{T}}$. The syntax of $\mathcal{L}^{\mathcal{A}}$ is given by the following Backus-Naur form:

$$\phi \;:=\; p \mid \neg\phi \mid \phi \vee \phi \mid \;\Diamond\, \phi \mid \phi \rightsquigarrow \phi$$

where $p \in \Phi^{\mathcal{T}}$. The standard abbreviations for the classical connectives $\wedge, \rightarrow, \leftrightarrow$ are usedin addition, it is convenient to use:

$$\Box\phi \;:=\; \neg \Diamond \neg\phi \tag{9.15}$$

The semantics of $\mathcal{L}^{\mathcal{T}}$ are given recursively as per definitions 5.2 and 9.5; the semantics for the modal operators are:

$$\mathfrak{M}^{\mathfrak{T}}, c \Vdash \Diamond\phi \text{ iff } \mathfrak{M}^{\mathfrak{T}}, c' \Vdash \phi \text{ for some } c' \in C^{\mathfrak{T}} \text{ such that } cR^{\mathfrak{T}}c' \tag{9.16}$$

$$\mathfrak{M}^{\mathfrak{T}}, c \Vdash \phi \rightsquigarrow \psi \text{ iff } \forall c' \in M^{\mathfrak{T}}_{c/\phi} : \mathfrak{T}^{\mathfrak{T}}, c' \Vdash \psi \tag{9.17}$$

where $M^{\mathfrak{T}}_{c/\phi} \subseteq C^{\mathfrak{T}}$ is the set of maximally similar ϕ-codons with respect to c:

$$c' \in M^{\mathfrak{T}}_{c/\phi} \text{ iff } \mathfrak{M}^{\mathfrak{T}}, c' \Vdash \phi \text{ and } \neg\exists c'' \in C^{\mathfrak{T}} \text{ such that } c'' <_c^{\mathfrak{T}} c' \text{ and } \mathfrak{M}^{\mathfrak{T}}, c'' \Vdash \phi \tag{9.18}$$

9.5 Summary

I argue that the standard semantics of counterfactual conditionals are a bad fit for biological counterfactuals. The standard semantics require a similarity ordering of states which is explicated in terms of physical laws. However, such a similarity ordering is pragmatically unattainable, and even if it were attainable, it would still entail explanatory mismatches. As an alternative, I propose a similarity ordering in terms of edit distance that is easily computable. This yields semantics for at least some biological counterfactuals that does not rely on laws (physical or other). Finally, I show that these semantics can be seamlessly integrated with the semantics of the biological modalities introduced earlier.

Conclusion

In order to understand the epistemic role of biological modalities in biological explanations, a theory of biological modalities is required. Such a theory must provide truth conditions of biological modalities, enable an analysis of the inferential relationships between biological and other kinds of modalities, and take into account the heterogeneous nature of biological modalities by explicating how biological modalities can be graded. However, defining biological modalities in terms of (biological) laws turns out to be a blind alley. This leads to the three main results of this thesis: First, a sketch of a more promising alternative is constructed by improving upon Dennett's definition of biological possibility, summarized by in this schema: x is CE possible with respect to some genome g if and only if there is some genome g' such that x is an instance of g' or a feature of the phenotypic products of g', and there is an edit script from g to g' that fits certain cost requirements C given a set of edit operations E. Second, the potential of the sketched theory is demonstrated via an implementation within the framework of modal logic based on a case study of hemoglobin variants. And third, two applications of this implementation are provided, namely the model checking tool SMAC and a lawless semantics for biological counterfactuals. In short, this thesis lays the groundwork for a better understanding of the epistemic role of biological modalities in biological explanations. Possible future work mirrors the limitations of the presented results: The theory as stated can hardly account for biological modalities at larger scales, namely the population level or higher. Perhaps this limitation can be overcome by expanding the base of the above schema; more likely, however, a completely different approach is required. In addition, the given implementation is static and timeless whereas (most) biological phenomena are not. Here dynamic modal logics look promising. Finally, there is a rather straightforward application to conceptual issues involving biological constraints (e.g., Green and Jones 2016), biological functions and contrast classes (e.g., Wouters 2007), and dispositional notions of health (e.g., Werkhofen 2016).

Appendix

A. Geometric scaling

We show that surface area A of some animal is proportional to its mass m raised to the $\frac{2}{3}$ power:

$$A \propto m^{\frac{2}{3}} \tag{A.1}$$

For this, two assumptions are required. First, the three-dimensional shape of the animal is represented by a sphere. Let r be the radius of the sphere. Then its surface area and volume V of the are given by:

$$A = 4\pi r^2 \tag{A.2}$$

$$V = \frac{4}{3}\pi r^3 \tag{A.3}$$

Second, neglecting density, the animal's mass is proportional to its volume:

$$m \propto V \tag{A.4}$$

Now, by canceling the proportionality constants 4π and $\frac{4}{3}\pi$, (A.2) and (A.3) can be rewritten as:

$$A \propto r^2 \tag{A.5}$$

$$V \propto r^3 \tag{A.6}$$

If we solve (A.6) for r, we get:

$$V^{\frac{1}{3}} \propto r \tag{A.7}$$

By (A.5) and (A.7):

$$A \propto (V^{\frac{1}{3}})^2 \propto V^{\frac{2}{3}} \tag{A.8}$$

Finally, (A.1) follows from (A.4) and (A.8). It goes without saying that geometric scaling of animals is an idealization; for more realistic methods, see for example Wang and Hihara (2004).

B. Computable edit script

For a computable definition of edit scripts, replace definitions 3.23–3.24 with the following:

Definition B.1 (Computable edit script)
Let i, t be strings. An edit script $\mathcal{S}$ is a sequence of operations $\langle \mathcal{E}_1, \mathcal{E}_2, \ldots, \mathcal{E}_n \rangle$ where $n \in \mathbb{N}_1$. An application of $\mathcal{S}$ to i, denoted by $\mathcal{S}(i)$, builds a string via the serial application of operations to position $i(i)$ where $0 < i \leq |i|$. Set $t = \lambda$, $m = 1$ and $i = 1$. Then, for $\mathcal{E}_m = \langle x, y \rangle$ until $m = n$: If $x = y = \lambda$, set $t = t \oplus i[i]$, $m = m + 1$ and $i = i + 1$ (copy operation); if $x \neq \lambda$ and $y \neq \lambda$, set $t = t \oplus y$, $m = m + 1$ and $i = i + 1$ (substitution operation); if $x \neq \lambda$ and $y = \lambda$, set $m = m + 1$ and $i = i + 1$ (deletion operation); if $x = \lambda$ and $y \neq \lambda$, set $t = t \oplus y$ and $m = m + 1$ (insertion operation).

C. Modal logics

This section provides a brief introduction to propositional modal logics based on Blackburn et al. (2001). Let $\mathfrak{M} = \langle \mathfrak{R}, V \rangle$ be a model where $\mathfrak{R}$ is a relational structure as per definition 3.1 and V is a valuation function, and let $\mathcal{L}$ be an arbitrary modal language. Then a modal logic can be defined syntactically:

Definition C.1 (Modal logic, syntactic)
A modal logic $\mathbf{L}_\Gamma$ over a generator $\Gamma \subseteq \mathcal{L}$ is a set such that:

1. If $\phi \in \Gamma$, then $\phi \in \mathbf{L}_\Gamma$,
2. if $\phi \in \Gamma$ and ψ is an abbreviation of ϕ, then $\psi \in \mathbf{L}_\Gamma$,

3. if ϕ is a propositional tautology, then $\phi \in \mathbf{L}_\Gamma$,
4. if $\phi, \phi \rightarrow \psi \in \mathbf{L}_\Gamma$, then $\psi \in \mathbf{L}_\Gamma$, and
5. if $\phi \in \mathbf{L}_\Gamma$ and ψ is a substitution instance of ϕ, then $\psi \in \mathbf{L}_\Gamma$

Definition C.1 states that a modal logic over a generator contains 1. all sentences of the generator, 2. their abbreviations and 3. all propositional tautologies, and is closed under 4. modus ponens and 5. uniform substitution (Blackburn et al. 2001: 191f.). Concerning notation, $\mathbf{L}$ with or without subscript will be used as meta-variable for any modal logic; $\mathbf{N}$ with or without subscript will be used as meta-variable for any normal modal logic (see below); other bold uppercase Roman letters denote specific modal logics.

Two remarks with respect to the generator and propositional tautologies are in order. First, definition C.1 is an algorithm for constructing a modal logic based on a generator. Therefore, modal logics can be individuated by their generator: every element in the power set of a modal language can figure as generator and can hence be used to construct a modal logic. Second, sentences such as $\Diamond\phi \vee \neg \Diamond \phi$ are propositional tautologies even though they contain non-classical operators. In the light of the syntactic definition C.1, a modal logic is hence simply a classical propositional logic with the addition of the diamond-operator (and its dual, the box-operator).

In order to define a modal logic semantically, the notion of validity is required:

Definition C.2 (Validity)
That a sentence $\phi \in \mathcal{L}$ is valid in a relational structure $\mathfrak{R} = \langle D, R \rangle$ at an element $d \in D$ is written as $\mathfrak{R}, d \Vdash \phi$:

$$\mathfrak{R}, d \Vdash \phi \text{ iff } \mathfrak{M}, d \Vdash \phi \text{ for all models } \mathfrak{M} = \langle \mathfrak{R}, V \rangle \tag{C.1}$$

That ϕ is valid in $\mathfrak{R}$ is written as $\mathfrak{R} \Vdash \phi$:

$$\mathfrak{R} \Vdash \phi \text{ iff } \mathfrak{R}, d \Vdash \phi \text{ for all } d \in D \tag{C.2}$$

That ϕ is valid in a class of relational structures $[\mathfrak{R}]$ is written as $[\mathfrak{R}] \Vdash \phi$:

$$[\mathfrak{R}] \Vdash \phi \text{ iff } \mathfrak{R} \Vdash \phi \text{ for all } \mathfrak{R} \in [\mathfrak{R}] \tag{C.3}$$

Definition C.2 states that a sentence is valid at an element of a relational structure's domain if and only if it is true for all models over the relational structure (Blackburn et al. 2001: 24). That is, the relational structure is kept constant whereas the valuation is varied. A modal logic can now be defined semantically:

Definition C.3 (Modal logic, semantic)
A modal logic $\mathbf{L}_{[\mathfrak{R}]}$ of a class of relational structures $[\mathfrak{R}]$ is $\{\phi : [\mathfrak{R}] \Vdash \phi\} \subseteq \mathcal{L}$.

Definition C.3 states that a modal logic of a class of relational structures is the subset of sentences of a modal language that are valid on this class. The correspondence between syntactic and semantic definitions of modal logics is captured in terms of soundness and completeness (Blackburn et al. 2001: 195f.):

Definition C.4 (Soundness)
A modal logic $\mathbf{L}_\Gamma$ is sound with respect to a class of relational structures $[\mathfrak{R}]$ if $\mathbf{L}_\Gamma \subseteq \mathbf{L}_{[\mathfrak{R}]}$.

Definition C.5 (Completeness)
A modal logic $\mathbf{L}_\Gamma$ is complete with respect to a class of relational structures $[\mathfrak{R}]$ if $\mathbf{L}_{[\mathfrak{R}]} \subseteq \mathbf{L}_\Gamma$.

Definition C.4 states that a modal logic is sound with respect to a class of relational structures if all its sentences are valid on the class. That is, if all its sentences are true in all models over all relational structures of the class. Definition C.4 states that a modal logic is complete with respect to a class of relational structures if it contains all sentences that are valid on the class. Therefore, if a modal logic is sound and complete with respect to a class of relational structures, it contains exactly the sentences that are valid on the class.

Many important completeness results pertain to so-called normal modal logics. Here is a syntactic definition of normal modal logics:

Definition C.6 (Normal modal logic)
A normal modal logic $\mathbf{N}_\Gamma$ over a generator $\Gamma \subseteq \mathcal{L}$ is a modal logic $\mathbf{L}_\Gamma$ such that:

1. If $\phi \in \mathbf{L}_\Gamma$, then $\phi \in \mathbf{N}_\Gamma$,

2. $\Box(\phi \to \psi) \to (\Box\phi \to \Box\psi) \in \mathbf{N}_\Gamma$, and

3. if $\phi \in \mathbf{N}_\Gamma$, then $\Box\phi \in \mathbf{N}_\Gamma$

Definition C.6 states that a normal modal logic over a generator is the modal logic over the same generator that satisfies two additional constraints (Blackburn et al. 2001: 193f.): First, it must contain the K-axiom:

$$\Box(\phi \to \psi) \to (\Box\phi \to \Box\psi) \tag{C.4}$$

Second, it must be closed under necessitation. To be maximally explicit, a normal modal logic over a generator contains all propositional tautologies, all sentences of the generator (and their abbreviations), the K-axiom, and is closed under modus ponens, uniform substitution and necessitation.

Since modal logics can be individuated by their generator, normal modal logics can also be individuated by their generator. For example, **K** is the normal modal logic over the empty generator, and **K** is sound and complete with respect to the class of all relational structures.

At this point, it is unavoidable to say a few words about the confusing nomenclature of (normal) modal logics. That $\mathbf{N}_\varnothing$ is called **K** has analytic and historic reasons. The analytic reason is that **K** is the smallest normal modal logic; that is, it is the smallest modal logic that contains the K-axiom and is closed under necessitation. Historically, the K-axiom derives its name from the work of Saul Kripke (1959) who pioneered relational semantics of modal logics. The most straightforward algorithm to name normal logics in light of these two reasons is hence to add the names of the elements of the generator to **K** (Blackburn et al. 2001: 194). For example, take the T-axiom $\Diamond\phi \to \Diamond\Diamond\phi$. Then $\mathbf{KT} = \mathbf{N}_{\{\Diamond\phi\to\Diamond\Diamond\phi\}}$ is the normal modal logic over $\Gamma = \{\Diamond\phi \to \Diamond\Diamond\phi\}$. However, difficulties stem from the fact that the same axiom is known by different names. For example, the T-axiom is also known as M-axiom and by many other names (for an overview see Halleck 2013).

D. Graded models support

The basic functions for computing the numerical results in sections 6.2 and 6.3 (especially Figures 6.3–6.9) are briefly outlined as implemented in Python 2.7.9.

```
#Returns n for ◇!ⁿᵐp in the simple model at startcodon:
def diamond(startcodon, aminoacid, m):
    truthmakers = truthmakers(aminoacid)
    paths = paths(startcodon, m)
    counter = set()
    for path in paths:
        codon = path[(3*m):(3*m)+3]
        if codon in truthmakers:
            counter.add(codon)
    return len(counter)

#Returns n for ◇!ⁿᵐp in the simple model at startcodon:
def diamonddot(startcodon, aminoacid, m):
    truthmakers = truthmakers(aminoacid)
    paths = paths(startcodon, m)
    counter = 0
    for path in paths:
        codon = path[(3*m):(3*m)+3]
        if codon in truthmakers:
            counter += 1
    return float(counter)

#Returns ◇ᵐp=α in the constant resp. biased probabilistic
#model at startcodon:
def diamondprob(startcodon, aminoacid, m, selector):
    truthmakers = truthmakers(aminoacid)
    paths = paths(startcodon, m)
    sumoverpaths = float(0)
    for path in paths:
        codon = path[(3*m):(3*m)+3]
        if codon in truthmakers:
            pathproduct = product(path, selector)
            sumoverpaths = sumoverpaths + pathproduct
    return sumoverpaths

#Amino acids:
aminoacids = ['A', 'R', 'N', 'D', 'C', 'Q', 'E', 'G', 'H', 'I', 'L',
              'K', 'M', 'F', 'P', 'S', 'T', 'W', 'Y', 'V', '*']

#Returns codons at which aminoacid is true:
def truthmakers(aminoacid):
    if aminoacid == 'A':
        return set(['GCA', 'GCC', 'GCG', 'GCT'])
    if aminoacid == 'R':
        return set(['AGA', 'AGG', 'CGA', 'CGC', 'CGG', 'CGT'])
    if aminoacid == 'N':
        return set(['AAC', 'AAT'])
    if aminoacid == 'D':
        return set(['GAC', 'GAT'])
```

```
    if aminoacid == 'C':
        return set(['TGC', 'TGT'])
    if aminoacid == 'Q':
        return set(['CAA', 'CAG'])
    if aminoacid == 'E':
        return set(['GAA', 'GAG'])
    if aminoacid == 'G':
        return set(['GGA', 'GGC', 'GGG', 'GGT'])
    if aminoacid == 'H':
        return set(['CAC', 'CAT'])
    if aminoacid == 'I':
        return set(['ATA', 'ATC', 'ATT'])
    if aminoacid == 'L':
        return set(['CTA', 'CTC', 'CTG', 'CTT', 'TTA', 'TTG'])
    if aminoacid == 'K':
        return set(['AAA', 'AAG'])
    if aminoacid == 'M':
        return set(['ATG'])
    if aminoacid == 'F':
        return set(['TTC', 'TTT'])
    if aminoacid == 'P':
        return set(['CCA', 'CCC', 'CCG', 'CCT'])
    if aminoacid == 'S':
        return set(['AGC', 'AGT', 'TCA', 'TCC', 'TCG', 'TCT'])
    if aminoacid == 'T':
        return set(['ACA', 'ACC', 'ACG', 'ACT'])
    if aminoacid == 'W':
        return set(['TGG'])
    if aminoacid == 'Y':
        return set(['TAC', 'TAT'])
    if aminoacid == 'V':
        return set(['GTA', 'GTC', 'GTG', 'GTT'])
    if aminoacid == '*':
        return set(['TAA', 'TAG', 'TGA'])

#Returns all single substitutions for codon:
def substitutions(codon):
    alphabet = set(['A', 'C', 'G', 'T'])
    substitutions = set()
    i = 0
    while i < len(codon):
        for letter in alphabet:
            substitution = list(codon)
            substitution[i] = letter
            substitution = ''.join(substitution)
            substitutions.add(substitution)
        i += 1
    substitutions.remove(codon)
    substitutions = list(substitutions)
```

```
    return substitutions

#Returns all unique sequences of m single substitutions for
#startcodon:
def paths(startcodon, m):
    fullpaths = list()
    codons = substitutions(startcodon)
    for codon in codons:
        path = ''.join([startcodon, codon])
        fullpaths.append(path)
    depth = 1
    while depth < m:
        paths = fullpaths[:]
        fullpaths = list()
        for path in paths:
            codon = path[len(path)-3:len(path)]
            newpaths = substitutions(codon)
            for newpath in newpaths:
                fullpath = ''.join([path, newpath])
                fullpaths.append(fullpath)
        depth += 1
    return fullpaths

#Returns probability of a give sequence of single substitutions:
def product(path, selector):
    m = (len(path)/3)-1
    product = float(1)
    while m > 0:
        start = path[(3*m)-3:(3*m)]
        stop = path[(3*m):(3*m)+3]
        stopletter = 0
        for letter in start:
            if letter is not stop[stopletter]:
                startbase = letter
                stopbase = stop[stopletter]
            else:
                stopletter += 1
        product = product*probability(startbase, stopbase, selector)
        m -= 1
    return product

#Returns P of substitution in the constant resp. biased
#probabilistic model:
def probability(startbase, stopbase, selector):
    if selector == 'constant':
        return float(1)/9
    if selector == 'biased':
        transition = float(0.51)/3
        transversion = float(0.49)/6
```

```
if startbase == 'A':
    if stopbase == 'G':
        return transition
    else:
        return transversion
if startbase == 'G':
    if stopbase == 'A':
        return transition
    else:
        return transversion
if startbase == 'C':
    if stopbase == 'T':
        return transition
    else:
        return transversion
if startbase == 'T':
    if stopbase == 'C':
        return transition
    else:
        return transversion
```

E. First-order allele model

It is shown how the limitation to homozygous genes of the first-order generalized model $\mathfrak{M}^{\mathfrak{F}}$ respectively the first-order protein language $\mathcal{L}^{\mathcal{F}}$ discussed in section 7.2.1 can be overcome. This is achieved via a model that has pairs of alleles as states and a language that defines truth over several alleles. I start by defining the first-order allele model:

Definition E.1 (First-order allele model)
A first-order allele model $\mathfrak{M}^{\mathfrak{A}}$ is a octuple $\left\langle A^{\mathfrak{A}}, G^{\mathfrak{A}}, M^{\mathfrak{A}}, R_{\mu}^{\mathfrak{A}}, D_{g}^{\mathfrak{A}}, N^{\mathfrak{A}}, \Pi^{\mathfrak{A}}, V_{a}^{\mathfrak{A}}\right\rangle$ such that:

- $G^{\mathfrak{A}} = G^{\mathfrak{F}}$, $M^{\mathfrak{A}} = M^{\mathfrak{F}}$, $N^{\mathfrak{A}} = N^{\mathfrak{F}}$, and $\Pi^{\mathfrak{A}} = \Pi^{\mathfrak{F}}$.
- $A^{\mathfrak{A}} = G^{\mathfrak{A}} \times G^{\mathfrak{A}}$ is the set of allele pairs $a = \langle g, g' \rangle$.
- $D_{g}^{\mathfrak{A}}$ is the domain of quantification for each $g \in G^{\mathfrak{A}}$, .
- $R_{\mu}^{\mathfrak{A}} \subseteq A^{\mathfrak{A}} \times A^{\mathfrak{A}}$ is a binary relation for each class of point mutation $\mu \in M^{\mathfrak{A}}$ such that:

$$\langle g, g' \rangle R_{\mu}^{\mathfrak{A}} \langle g'', g''' \rangle \text{ iff } g R_{\mu}^{\mathfrak{F}} g'' \text{ and } g' = g''' \tag{E.1}$$

That is, the relation connects pairs of alleles where only one of the alleles is allowed to bear a point mutation. In other words, the relation is interpreted as ceteris paribus point mutation for heterozygous genes. Note that we might require $\langle g, g' \rangle$ (but not $\langle g'', g''' \rangle$) to be an actual allele pair/heterozygous gene.

- $V^{\mathfrak{A}}_{\langle g,g' \rangle}$ is a valuation function for each $\langle g, g' \rangle \in A^{\mathfrak{F}}$ such that:

$$V^{\mathfrak{A}}_{\langle g,g' \rangle}(\xi) = \begin{cases} \langle d \in D^{\mathfrak{A}}_g, d' \in D^{\mathfrak{A}}_{g'} \rangle & \text{if } \xi \in N^{\mathfrak{A}} \\ \langle S \subseteq (D^{\mathfrak{A}}_g)^n, S' \subseteq (D^{\mathfrak{A}}_{g'})^n \rangle & \text{if } \xi \in \Pi^{\mathfrak{A}} \end{cases} \tag{E.2}$$

Square brackets as in $V^{\mathfrak{A}}_{\langle g,g' \rangle}(\xi)[n]$ are used to denote the n-th element of $V^{\mathfrak{A}}_{\langle g,g' \rangle}(\xi)$.

Note that the first-order allele model employs varying domains instead of a constant domain as employed be the first-order generalized model. I now define the first-order allele language:

Definition E.2 (First-order allele language)
First-order allele models $\left\langle A^{\mathfrak{A}}, G^{\mathfrak{A}}, M^{\mathfrak{A}}, R^{\mathfrak{A}}_{\mu}, D^{\mathfrak{A}}_g, N^{\mathfrak{A}}, \Pi^{\mathfrak{A}}, V^{\mathfrak{A}}_a \right\rangle$ are described via the first-order protein allele language $\mathcal{L}^{\mathcal{A}}$. The syntax of $\mathcal{L}^{\mathcal{A}}$ is given by the following Backus-Naur form:

$$\phi \coloneqq P^{\mathscr{S}}(t_1, \ldots, t_n) \mid \neg\phi \mid \phi \vee \phi \mid \Diamond_{\mu} \phi \mid \exists x \phi$$

where $P(t_1, \ldots, t_n) \in \Pi^{\mathfrak{A}}$, $\mathscr{S} \in \{\lambda, \text{and}, \text{or}, \text{xor}, \ldots\}$, and $\mu \in M^{\mathfrak{A}}$. The standard abbreviations for the classical connectives $\wedge, \rightarrow, \leftrightarrow$ are used; the abbreviations $\Box_{\mu}$, $\langle M \rangle$, $[M]$, and $\forall x$ are used as per definition 7.4 That a formula ϕ of $\mathcal{L}^{\mathcal{A}}$ is true in $\mathfrak{M}^{\mathfrak{A}}$ under assignment $\bullet$ an allele pair $a = \langle g, g' \rangle \in A^{\mathfrak{A}}$ is written as $\mathfrak{M}^{\mathfrak{A}}, \bullet, a \Vdash \phi$. Let $\bullet$ be an assignment such that:

$$\bullet(t) = \begin{cases} V^{\mathfrak{A}}_a(t) & \text{if } t \in N^{\mathfrak{A}} \\ \langle d \in D^{\mathfrak{A}}_g, d' \in D^{\mathfrak{A}}_{g'} \rangle & \text{otherwise} \end{cases} \tag{E.3}$$

Square brackets as in $V \bullet (t)[n]$ are used to denote the n-th element of $\bullet(t)$. The semantics of $\mathcal{L}^{\mathcal{A}}$ are given recursively (restricted to 1-ary predicates for ease of

presentation):

$$\mathfrak{M}^{\mathfrak{A}}, \bullet, a \Vdash P^{\mathscr{S}}(t) \text{ iff } \begin{cases} \bullet(t)[1] \in V_a^{\mathfrak{A}}(P)[1] & \text{if } \mathscr{S} = \lambda \\ \bullet(t)[1] \in V_a^{\mathfrak{A}}(P)[1] \mathscr{S} \bullet(t)[2] \in V_a^{\mathfrak{A}}(P)[2] & \text{otherwise} \end{cases} \tag{E.4}$$

$$\mathfrak{M}^{\mathfrak{A}}, \bullet, a \Vdash \neg\phi \text{ iff not } \mathfrak{M}^{\mathfrak{A}}, \bullet, a \Vdash \phi \tag{E.5}$$

$$\mathfrak{M}^{\mathfrak{A}}, \bullet, a \Vdash \phi \vee \psi \text{ iff } \mathfrak{M}^{\mathfrak{A}}, \bullet, a \Vdash \phi \text{ or } \mathfrak{M}^{\mathfrak{A}}, \bullet, a \Vdash \phi \tag{E.6}$$

$$\mathfrak{M}^{\mathfrak{A}}, \bullet, a \Vdash \Diamond_\mu \phi \text{ iff } \mathfrak{M}^{\mathfrak{A}}, \bullet, a' \Vdash \phi \text{ for some } a' \in A^{\mathfrak{A}} \text{ such that } a R_\mu^{\mathfrak{A}} a' \tag{E.7}$$

$$\mathfrak{M}^{\mathfrak{A}}, \bullet, a \Vdash \exists x \phi \text{ iff } \mathfrak{M}^{\mathfrak{A}}, \bullet', a \Vdash \phi \text{ for some } \bullet' \text{ such that } \bullet' \sim_x \bullet \tag{E.8}$$

where $\bullet' \sim_x \bullet$ if $\bullet'(y) = \bullet(y)$ for all y such that $y \neq x$. That a formula ϕ of $\mathcal{L}^{\mathcal{A}}$ is true in $\mathfrak{M}^{\mathfrak{A}}$ at pair of alleles $a \in A^{\mathfrak{A}}$ is written as $\mathfrak{M}^{\mathfrak{A}}, a \Vdash \phi$ and defined by:

$$\mathfrak{M}^{\mathfrak{A}}, a \Vdash \phi \text{ iff } \mathfrak{M}^{\mathfrak{A}}, \bullet, a \Vdash \phi \text{ for all } \bullet \tag{E.9}$$

For illustration, consider two forms of beta thalassemia, namely beta thalassemia major and beta thalassemia minor. The former requires both alleles to be affected, the latter requires exactly one. Beta thalassemia can be caused in many different ways; an example is HBB:c.48G ⇝ A (with HbVar ID 793 which I will use as an identifier). It is caused by the substitution of guanine with adenine at codon 15 of *HBB*, resulting in a stop codon. Take the predicate $BetaThalassemia(t)$ and interpret it as 't causes beta thalassemia'. Now consider the following sentences:

$$\mathfrak{M}^{\mathfrak{A}}, \langle HBB, HBB \rangle \nVdash \exists x BetaThalassemia^{\text{and}}(x) \tag{E.10}$$

$$\mathfrak{M}^{\mathfrak{A}}, \langle HBB, 793 \rangle \nVdash \exists x BetaThalassemia^{\text{and}}(x) \tag{E.11}$$

$$\mathfrak{M}^{\mathfrak{A}}, \langle 793, 793 \rangle \Vdash \exists x BetaThalassemia^{\text{and}}(x) \tag{E.12}$$

So in $\mathcal{L}^{\mathcal{A}}$, we can express that beta thalassemia major is (not) caused by taking our predicate and letting it being evaluated at both alleles. For the super truth conditions, we can use standard logical connectives such as 'and' in (E.10)–(E.12) the case. By using 'xor' instead, we can express that beta thalassemia minor is caused:

$$\mathfrak{M}^{\mathfrak{A}}, \langle HBB, HBB \rangle \nVdash \exists x BetaThalassemia^{\text{xor}}(x) \tag{E.13}$$

$$\mathfrak{M}^{\mathfrak{A}}, \langle HBB, 793 \rangle \Vdash \exists x BetaThalassemia^{\text{xor}}(x) \tag{E.14}$$

$$\mathfrak{M}^{\mathfrak{A}}, \langle 793, 793 \rangle \nVdash \exists x BetaThalassemia^{\text{xor}}(x) \tag{E.15}$$

Other predicates such as $Lethal(t)$ used in subsection 7.2.1 can be defined in a similar fashion.

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Summary

Chapter 1 I argue that there is a tension between (1) the lack of philosophical interest in biological modalities and (2) the important explanatory role biological modalities play in biological practice. The first claim is supported by a quantitative analysis of major academic databases and a qualitative survey of the philosophical literature. I defend the second claim by four 'arguments from case study' pertaining to coiled ammonoid shell form, sticky footpads and maximum body size, the minimal bacterial genome and essential genes, and the habitability of exoplanets. I propose that a theory or logic of biological modalities could fill the epistemic lacunae between (1) and (2) by providing truth-conditions for biological modalities, shedding light on the relationship between biological and other modalities, and spelling out how biological modalities can be graded.

Chapter 2 I offer two main of clarifications of how (not) to think about biological modalities. First, I argue that defining biological possibility as non-violation of biological laws is problematic since it requires a commitment to both realism about biological laws and the better best systems account of special science laws; otherwise biological possibility is reduced to physical or logical possibility, or its definition is rendered circular. Second, I examine three ideas regarding the grading of (biological) possibility, namely (1) the distinction between kinds of possibility such as logical, physical and biological possibility and (2) between subkinds of biological possibility which roughly map to the scale of biological phenomena under investigation and come in historical or ahistorical flavors, and (3) the observation that some subkinds of biological possibility are comparative.

Chapter 3 I improve upon Daniel Dennett's definition of biological possibility by proposing two modifications. First, I provide a clarification of his definition by reconstructing the Library of Mendel as relational structure. Second, I argue that the most important shortcoming of Dennett's definition, namely the underdefined accessibility relation, can be overcome by interpreting the accessibility relation as a solution to a string editing problem. According to the restated definition, x is biologically possible with respect to a genome g if and only if there is some genome g' such that there is an edit script from g to g' that fits certain cost requirements given a set of edit operations, and

x is an instance of g or a feature of the phenotypic products of g'. This new definition is promising because it is rooted in biological practice and can be extended into a family of modal logics.

Chapter 4 I propose to put into action the results obtained so far by constructing logical models of hemoglobin variants. Hemoglobin is the protein in red blood cells responsible for binding oxygen; normal adult hemoglobin consists of two alpha and beta globin chains determined by the hemoglobin alpha and beta gene respectively. The modeling goal is to attain the desiderata specified above (to wit, truth conditions, inferential relationships, grading). To this end, I present a schema for the classification of point mutations and impose three modeling restrictions: The hemoglobin variants must be caused by (1) single (2) substitutions (3) at codon 6 of the hemoglobin beta gene. Finally, I briefly review why bioambient calculus, Zsyntax, and mathematical models in molecular biology are not suitable for the task at hand.

Chapter 5 I introduce a simple model of hemoglobin variants caused by single substitutions at codon 6 of the hemoglobin beta gene within the framework of propositional modal logic. In the model, states are interpreted as codons, the binary relation is interpreted as single substitution, and the valuation is kept fixed and induces a partition of blocks of codons that code for some amino acid. I argue that explicit truth conditions for at least historical and ahistorical biological modalities are attained via the modal language describing the model. This gives rise to a normal modal logic that is sound and complete with respect to the class of serial, symmetric and dense frames. After showing that the model can be simplified via bisimulation contraction, I argue that the notion of silent mutation is ambiguous between mutants that are bisimilar to the wild type and hence modally inert, and mutants that are not and hence modally active.

Chapter 6 I extend the simple model and language to account for comparative (historical) biological possibility. This yields a ranking of hemoglobin variants $v, v', \ldots$ caused by single substitutions at codon 6 of the hemoglobin beta gene. I distinguish four circumstances under which v is more possible than v': (1) v is easier to bring about that v', implemented by a modal operator capturing Hamming distance. (2) There are more possible v than v', implemented by a modal operator counting variants. (3) There are more ways to realize v than v', implemented by a modal operator counting unique sequences of single substitutions. (4) v is more probable than v', implemented by a non-epistemic probabilistic modal operator and a weighted binary relation interpreted as single substitution. In addition, I discuss the conditions for the introduced modal operators' loss of historical or local context, and I show the extension's ability to incorporate transition/transversion bias or amino acid scoring matrices.

Chapter 7 I show that the previously imposed modeling restrictions can be lifted via a generalization of the simple model. This enables the construction of logical models of any protein variant caused by any point mutation at the coding region of any gene. In the generalized model, states are interpreted as genes, multiple binary relations are interpreted as distinct point mutations, and the valuation is kept fixed and induces a partition of blocks of genes that code for some protein. I identify two limitations, namely (1) the limited expressive power and (2) the reliance on opaque modalities of the language describing the generalized model.

Chapter 8 I present SMAC (Simple Model Amino acid Checker), a model checking tool implemented in Python and made publicly available at maxghuber.github.io/SMAC under the Apache License. It allows the user to obtain the truth value of any formula ϕ of the basic amino acid language in the simple model. SMAC builds a semantic tree where the root is the codon of evaluation decorated with ϕ, descendants are codons decorated with subformulas of ϕ, and the leafs jointly comprise all logically possible truth makers of ϕ. Each branch is then evaluated bottom-up. I show that SMAC has the total correctness property, and that SMAC scales exponentially for nested modal operators where the exponent is given by the highest number of nested modal operators.

Chapter 9 I argue that the standard semantics of counterfactual conditionals are a bad fit for biological counterfactuals. The standard semantics require a similarity ordering of states which is explicated in terms of physical laws. However, such a similarity ordering is pragmatically unattainable, and even if it were attainable, it would still entail explanatory mismatches. As an alternative, I propose a similarity ordering in terms of edit distance that is easily computable. This yields semantics for at least some biological counterfactuals that does not rely on laws (physical or other). Finally, I show that these semantics can be seamlessly integrated with the semantics of the biological modalities introduced earlier.

Résumé

Cette thèse de doctorat a pour sujet les modalités biologiques. Les modalités biologiques sont des modalités comme la nécessité, la possibilité ou la contrefactualité qui portent sur des objets biologiques comme des écosystèmes, des populations, des organismes, des traits, des cellules ou des gènes. Par exemple, les auteurs d'un livre de cours standard de la biologie moléculaire écrivent qu'une « molécule comme l'hémoglobine était nécessaire pour permettre aux animaux multicellulaires de grandir jusqu'à une taille grande, car les grands animaux ne peuvent plus utiliser la diffusion d'oxygène par la surface des leurs corps pour oxygéner leurs tissus » (Alberts et al. 2008: 256, ma traduction). Cet énoncé contient trois modalités biologiques : la nécessité biologique (une molécule qui apporte l'oxygène d'appareil respiratoire au tissu du corps entier est une nécessité biologique pour les grands animaux multicellulaires), la possibilité biologique (même si l'hémoglobine est la molécule effective qui transporte l'oxygène dans les grands animaux multicellulaires, il est biologiquement possible que cette fonction soit assurée par une protéine différente), et la contrefactualité biologique (si les grands animaux multicellulaires n'avaient pas une molécule qui transporte l'oxygène, ils ne seraient pas viables).

Dans ce travail de thèse, j'adopte une perspective épistémique sur les modalités biologiques. Cela signifie que je développe des outils conceptuels qui ont pour but une compréhension améliorée du rôle explicatif des modalités biologiques. Si mes résultats portent aussi sur des questions métaphysiques ou ontologiques, c'est un accident heureux.

Ma thèse est organisée en trois parties. Dans les chapitres 1 à 3, je conçois une théorie des modalités biologiques. Dans les chapitres 4 à 7, je mets en place une implémentation de cette théorie dans le cadre de la logique modale et basée sur l'exemple des variantes d'hémoglobine. Finalement, dans les chapitres 8 et 9, je discute quelques applications de la théorie et de son implémentation. Je présente ci-dessous un résumé de chaque chapitre.

Motivation

Dans ce chapitre je révèle un désaccord entre (1) l'absence d'intérêt théorique pour les modalités biologiques et (2) le rôle explicatif important des modalités biologiques dans la pratique de la biologie contemporaine.

L'affirmation (1) est soutenue par deux arguments. Premièrement, une analyse quantitative des dix-neuf bases de données académiques les plus importantes (voir tableau 1.1) montre que la fréquence absolue des modalités biologiques est faible (voir tableau 1.3) et aussi que la fréquence des modalités biologiques relative aux fréquences des modalités logiques et physiques est faible (voir figure 1.1). Soit dit en passant, cette analyse nécessite une opérationnalisation des modalités en termes de chaines de caractères qui permet une analyse des bases de données académiques (voir tableau 1.2) et une normalisation des fréquences (voir tableau 1.4). Deuxièmement, une analyse qualitative de la littérature philosophique révèle une seule définition explicite des modalités : la définition de la possibilité biologique de Daniel Dennett (1995). En bref, Dennett définit la possibilité biologique comme relation entre génomes dans l'espace logique des génomes. Les avantages et les faiblesses de cette définition sont discutés en détail dans le chapitre 3. La combinaison des deux résultats indique l'absence d'intérêt théorique pour les modalités biologiques.

Je défends l'affirmation (2) par des arguments d'exemple. Un argument d'exemple est un argument ampliatif de la forme suivante :

P1 Un exemple X est représentatif d'un domaine scientifique D.

P2 Une proposition p est vraie dans X.

$\therefore$ Donc p est vraie dans D.

Voici le schéma d'argument d'exemple pertinent pour ce chapitre :

P1 Un exemple X est représentatif de la biologie.

P2 Les modalités biologiques jouent un rôle explicatif important dans X.

$\therefore$ Donc les modalités biologiques jouent un rôle explicatif important en biologie.

Le soutien de la conclusion dépend de la convergence de l'exemple avec le domaine scientifique : plus l'exemple est une représentation fidèle du domaine, plus la probabilité que la proposition soit vraie dans le domaine est grande. Comme difficulté additionnelle,

la biologie est un domaine hétérogène qui s'étend de l'exobiologie jusqu'à la zoologie. Marie Kaiser (2013) distingue trois classes d'exemples représentatifs : les exemples historiques, les exemples pédagogiques et les exemples de l'actualité de la recherche. Dans la suite, je me focalise sur un exemple historique, les coquilles spirales d'ammonoïdes, et trois exemples de l'actualité de la recherche : les pieds adhésifs et la taille maximale, le génome minimal et les gènes essentiels, et l'habitabilité sur les exoplanètes. Ces exemples couvrent l'exobiologie, la biomécanique, l'écologie, la biologie d'évolution, la biologie moléculaire et la biologie synthétique. Je suppose donc que l'argument d'exemple est une forme d'argument praticable et que la première prémisse est satisfaite pour chaque exemple. Je vais maintenant établir brièvement la deuxième prémisse (soit le rôle explicatif important des modalités biologiques) pour chaque exemple.

Première exemple. David Raup (1962, 1966, 1965, 1967) a simulé par ordinateur la croissance des coquilles spirales d'ammonoïdes. Une coquille spirale est modélisée par un cône creux qui tourne autour un axe fixe. L'espace morphologique des coquilles spirales est construit en modifiant pas à pas les valeurs des variables pertinentes (voir figure 1.2a). Or seulement une petite région de l'espace morphologique est occupée par des ammonoïdes (voir figure 1.2b). Raup explique que les autres régions sont « physiologiquement impossibles » (1966: 1185, ma traduction) ou « géométriquement possibles mais biologiquement impossibles » (1965: 1294, ma traduction).

Le deuxième exemple concerne le traveDavid Labonte et al. (2016) enquêtent sur la relation des pieds adhésifs à la taille des animaux de plus de 250 espèces. Des animaux comme les geckos ou les mites ont des pieds adhésifs qui leur permettent « de monter des surfaces lisses verticales » (Labonte et al. 2016: 1297, ma traduction). Labonte et al. trouvent une allométrie positive forte de la surface des tampons des pieds adhésifs et en concluent qu'une telle croissance est biologiquement impossible pour l'humain.

Troisième exemple. Clyde Hutchison et al. (2016) affirment avoir conçu et synthétisé le génome bactérien minimal qui se compose exactement des gènes essentiels ou nécessaires pour le développement autonome et la reproduction des bactéries.

Quatrième exemple. Charles Cockell et al. (2016) proposent une nouvelle définition du concept de l'habitabilité : un environnement E sur une exoplanète est habitable si et seulement si il existe un organisme connu, tant qu'il est possible pour cet organisme de vivre dans E.

Ainsi l'argument d'exemple montrent que les modalités biologiques jouent un rôle explicatif important dans les sous-domaines de la biologie considérés ci-dessus.

En conclusion, je propose qu'une théorie des modalités biologiques pourrait résoudre la lacune épistémique entre (1) et (2) car elle pourrait fournir les conditions de vérité pour les modalités biologiques, illuminer les relations inférentielles entre les modalités biologiques et les autres modalités (à savoir les modalités logiques et physiques), et montrer la manière dont les modalités biologiques peuvent être classées.

Clarifications

Dans ce chapitre je clarifie deux traits importants des modalités biologiques. Tout d'abord je rejette une définition populaire de la possibilité biologique. Puis je présente une distinction entre trois types de classification de la possibilité biologique.

Commençons avec une définition populaire de la possibilité biologique :

Definition R.1 (Possibilité biologique)
Une proposition ϕ est biologiquement possible si et seulement si l'ensemble de ϕ et des lois de la biologie est cohérent.

La definition R.1 est motivée par la définition suivante :

Definition R.2 (Possibilité logique)
Une proposition ϕ est logiquement possible si et seulement si l'ensemble de ϕ et des lois de la logique est cohérent.

Plus généralement, les définitions R.1 et R.2 sont des instances du schéma suivant :

Definition R.3 (Possibilité scientifique)
Soit S une science au sens large. Une proposition ϕ est S-possible si et seulement si l'ensemble de ϕ et des lois de S est cohérent.

La définition R.2 est peu problématique car les notions des lois de la logique et de la cohérence d'un ensemble sont bien définis (bien sûr, la signification exacte des lois de la logique dépend du formalisme en jeu et de savoir si un pluralisme logique est vrai ou non). Par contraste, la notion de lois de la biologie est très controversée. Or, considérons un dilemme : pour n'importe quelle théorie courante des lois de la biologie T, (1) T implique une réduction de la définition R.1 à la définition R.2 ou à une instance de R.3 où S est

identifiée comme science fondamentale (i.e. la physique), ou (2) T rend circulaire la définition R.1. Ni (1) ni (2) ne sont acceptables : la proposition (1) n'est pas acceptable car l'existence (ou au moins l'importance explicative) de la possibilité biologique est rejetée ; la proposition (2) n'est pas acceptable car notre but est une explication de la possibilité biologique.

Voici les arguments en faveur de (1) : ce problème porte sur les théories antiréalistes des lois biologiques. Il y en a de deux espèces. Premièrement les théories qui nient l'existence des lois biologiques. Par exemple, John Beatty (2006) défend, sur la base de la thèse de la contingence de l'évolution, que les lois biologiques n'existent pas. Mais ϕ est trivialement cohérent avec l'ensemble vide si ϕ n'est pas une contradiction. Donc la définition R.1 est réduite à la définition R.2. Deuxièmement, les théories qui argumentent pour une réduction des lois biologiques aux lois de la physique (bien entendu ce réductionnisme connaît plusieurs versions, par exemple le réductionnisme conservatif de Christian Sachse 2012). Si les lois de la biologie ne sont rien d'autre que les lois de la physique, alors la possibilité biologique est réduite à la possibilité physique.

Considérons maintenant les arguments en faveur de (2). Ce problème porte sur les théories réalistes des lois biologiques qui expliquent la notion de loi en termes de modalités. Il y en a de deux espèces. Premièrement les théories qui expliquent une loi en termes de modalités primitives. Par exemple, la théorie manipulationiste de James Woodward (2003) est basée sur des conditionnels contrefactuels du même objet (anglais : same object counterfactuals) qui sont primitifs. Mais si les lois biologiques sont expliquées en termes des modalités primitives, et si la possibilité biologique est expliquée en termes de lois biologiques, alors la possibilité biologique est expliquée en termes de modalités primitives. Ce résultat est peu utile. Deuxièmement, les théories qui expliquent une loi en termes de modalités biologiques. Par exemple, Chris Haufe (2013) propose que les lois de la biologie soient des chances nécessaires qui sont dérivées de lois mathématiques, le caractère biologique ne concernant que leur interprétation. Ici la circularité est évidente.

La seule théorie populaire des lois qui n'est pas affectée par ce dilemme est la théorie des meilleurs meilleurs systèmes (anglais : better best systems) de Markus Schrenk (2007) et Jonathan Cohen et Craig Callender (2009) ; mais cette théorie présente d'autres problèmes graves (voir par exemple Backmann and Reutlinger 2014). Donc la définition R.1 n'est pas accessible ou requiert une profession de foi en faveur de la théorie des meilleurs meilleurs systèmes. Une alternative plus viable sera développée dans le chapitre 3.

Considérons maintenant la deuxième clarification. Au premier abord la notion d'une classification de la possibilité biologique concerne plusieurs projets. (1) La distinction entre différents types de possibilité comme la possibilité logique, la possibilité physique et la possibilité biologique. Comment peut-on caractériser les relations inférentielles entre ces types de possibilité ? Supposons que la possibilité physique et la possibilité biologique requièrent la possibilité logique mais pas l'inverse. Alors la relation inférentielle entre la possibilité physique et la possibilité biologique est soit indépendante, soit partielle, soit asymétrique, soit symétrique (pour plus des détails, voir figure 2.1). (2) La distinction entre différents types de possibilité biologiques. Par exemple, la possibilité biologique historique n'est pas identique à la possibilité biologique stricte, et la possibilité biologique des molécules n'est pas identique à la possibilité biologique des biosphères (pour plus des détails, voir figure 2.2). (3) La possibilité biologique comparative dans le cadre d'un domaine de possibilité. Par exemple, dans le cadre de l'espace morphologique des coquilles spirales des ammonoïdes, les coquilles spirales sans recouvrement sont biologiquement plus possibles que les coquilles spirales chevauchantes (voir ci-dessus). Cette notion est discutée en détail au chapitre 6.

La possibilité biologique selon Dennett

Daniel Dennett propose (et il peut-être le seul à le faire, voir chapitre 1) une définition explicite de la possibilité biologique :

Definition R.4 (Possibilité biologique)
« x est biologiquement possible si et seulement si x est une instance d'un génome accessible [dans la Bibliothèque de Mendel] ou une propriété des produits phénotypiques de ce génome » (1995: 118, ma traduction) où la Bibliothèque de Mendel est « l'espace logique de tous les génomes » (1995: 123, ma traduction).

Le but de ce chapitre est de proposer en deux étapes une amélioration de cette définition. Premièrement, j'exprime une version plus précise de la définition R.4 qui est fondée sur une reconstruction de la Bibliothèque de Mendel comme structure relationnelle :

Definition R.5 (Bibliothèque de Mendel)
La Bibliothèque de Mendel est une structure relationnelle $\langle \Sigma, R \rangle$ où :

- Le domaine Σ est la fermeture de Kleene de l'alphabet $\{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}$ où $\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}$ représentent les nucléotides (adénine, cytosine, guanine ou thymine). Intuitivement le domaine comprend tous les génomes qui sont logiquement possible étant donné $\{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}$.
- $R \subseteq \Sigma \times \Sigma$ est une relation binaire interprétée comme relation d'accessibilité.

Pour plus de détails, voir les définitions 3.1–3.20.

La définition R.5 permet une précision de la définition R.4 :

Definition R.6 (Possibilité biologique)
N'importe quel x est biologiquement possible à $g \in \Sigma$ si et seulement si il existe un $g' \in \Sigma$ où gRg' et x est une instance de g' ou une propriété des produits phénotypiques du g'.

Deuxièmement, j'identifie plusieurs problèmes avec la définition R.6 : savoir si l'hypothèse implicite de la définition d'un « lecteur-constructeur » (Dennett 1995: 113, ma traduction) qui transforme les génomes en produits phénotypiques est une abstraction ou une idéalisation, l'absence de l'environnement dans la définition, et l'ambiguïté de la définition entre les individus et les populations. Or le problème principal de la définition R.6 est le fait que la relation d'accessibilité n'est pas définie. Autrement dit on ne sait pas si gRg' à moins que g ait accès à g'. Mais qu'est-ce que cela signifie ? Je propose de résoudre ce problème par une interprétation de la relation d'accessibilité dans le cadre de l'édition de chaînes de caractères.

Voici la définition de la distance d'édition :

Definition R.7 (Distance d'édition)
Soit s, s' des chaînes de caractères, $\gamma : E \to \mathbb{R}_+$ la fonction de coût pour l'ensemble des opérations d'édition $E = \{\mathcal{E}, \mathcal{E}', \dots\}$, et $\mathcal{S} = \langle \mathcal{E}_1, \mathcal{E}_2, \dots, \mathcal{E}_n \rangle$ un script d'édition (voir la définition 3.23 pour l'operation d'édition et définition 3.24 pour le script

d'édition). La distance d'édition de s à s' est notée $\delta(s, s')$:

$$\delta(s, s') = \begin{cases} \min\{\gamma(\mathcal{S}) : s \xrightarrow{\mathcal{S}} s'\} & \text{si } |\{\gamma(\mathcal{S}) : s \xrightarrow{\mathcal{S}} s'\}| > 0 \\ \text{indéfini} & \text{autrement} \end{cases} \tag{R.1}$$

où

$$\gamma(\mathcal{S}) = \sum_{i=1}^{n} \gamma(\mathcal{E}_i) \tag{R.2}$$

Donc nous obtenons le schéma :

Definition R.8 (Relation d'accessibilité)
Pour $g, g' \in \Sigma$: gRg' si et seulement si $\delta(g, g') \leq \alpha$ où $\alpha \in \mathbb{R}_+$.

La définition R.8 est un schéma car la signification de la relation d'accessibilité dépend de la sensibilité α et du concept de la distance d'édition et ce concept dépend des opérations d'édition disponibles et de la fonction de coût respective. Par exemple, supposant $\alpha = 1$, R entendue en termes de la distance de Hamming n'est pas identique à R entendue en termes de la distance de Levenshtein.

En conclusion, les résultats des deux étapes présentées (soit la reformulation de la définition de la possibilité biologique de Dennett basée sur une structure explicitement relationnelle et l'interprétation de la relation d'accessibilité dans le cadre de l'édition de chaînes de caractères) ont un avantage clair : ils constituent un point de départ à la construction de modèles logiques pour rendre la signification des modalités biologiques en accord avec les desiderata formulés au chapitre 1.

Préliminaires de la modélisation logique

Dans les chapitres 5 à 7 je mets en pratique les résultats obtenus jusqu'à présent à partir d'une étude de cas détaillée. Ce cas concerne la construction des modèles logiques des variantes de l'hémoglobine en accord avec les desiderata formulés au chapitre 1 (soit les conditions de vérité, les relations inférentielles, la classification). L'hémoglobine est une protéine dans les globules rouges responsable du transport de l'oxygène et donc fonctionnellement associée à la respiration. Chez l'humain l'hémoglobine normale adulte se compose de deux chaînes de la globine alpha et de deux chaînes de la globine beta

qui sont déterminées par le gène *HBA* et par le gène *HBB* respectivement (voir Berg et al. 2012: 195–213 et figure 4.1). Or les modèles requis sont plutôt complexes : il y a au moins 1226 variantes connues de l'hémoglobine selon la base de données HbVar (avril 2016, voir Giardine et al. 2014). Pour réduire la complexité des modèles, j'impose donc trois restrictions.

Premièrement, les modèles sont limités à des variantes de l'hémoglobine causées par des mutations ponctuelles singulières (voir figure 4.2 pour une classification des mutations ponctuelles). Deuxièmement, les modèles sont limités à des variantes de l'hémoglobine causées par des mutations des nucléotides 19–21 (soit le codon 6) de la séquence codante du gène *HBB*. La séquence des nucléotides du codon 6 est `GAG` et encode la glutamine. Du point de vue de la modélisation logique, ce choix est arbitraire ; mais le codon 6 est biologiquement intéressant : la variante de l'hémoglobine HbS causée par une substitution de l'adénine à la thymine au nucléotide 20 est de la forme la plus fréquente de la drépanocytose (Rees et al. 2010: 2020). Finalement, les mutations de décalage de trame sont exclues pour des raisons de simplicité.

Conjointement ces trois restrictions définissent donc la tâche suivante : la construction des modèles logiques des variantes de l'hémoglobine causées par des substitutions singulières au codon 6 du gène *HBB*.

Modèle simple

Dans le cadre de la logique modale propositionnelle (Blackburn et al. 2001), j'introduis un modèle logique des variantes de l'hémoglobine causées par des substitutions singulières au codon 6 du gène *HBB*. Je commence avec la définition du modèle simple :

Definition R.9 (Modèle simple)
Un modèle simple $\mathfrak{M}$ est un quadruple $\langle C, R, \Phi, V\rangle$ où :

- C est l'ensemble des codons. Un codon $c \in C$ est représenté par une chaîne de caractères sur l'alphabet $\{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}$ où $|c| = 3$.
- $R \subseteq C \times C$ est une relation binaire interprétée comme substitution singulière dans le sens biologique.
- Φ est l'ensemble des propositions atomiques interprété comme l'ensemble des

acides aminés. Les minuscules p, q sans ou avec indices sont les variables de Φ ; les majuscules $\mathsf{A}, \mathsf{R}, \ldots$ dénomment les acides aminés correspondantes (voir tableau 4.2).

- $V : \Phi \to \mathcal{P}(C)$ est une fonction d'évaluation qui assigne un ensemble des codons $V(p) \subseteq C$ à chaque proposition atomique $p \in \Phi$. Intuitivement, l'évaluation indique pour chaque acide aminé les codons qui l'encodent.

Dans le modèle simple, le niveau d'ADN est encodé par le cadre (soit le domaine C avec la relation binaire R) alors que le niveau des protéines est encodé par l'évaluation. Notez que seule une évaluation est adéquate du point de vue empirique et que les autres évaluations sont ignorées par la suite. Cette évaluation produit une partition de l'ensemble des codons. La représentation graphique du modèle simple est difficile à cause de la taille du domaine $|C| = |\{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}|^{|c|} = 4^3 = 64$ et de la taille de la relation binaire $|R| = 64 \times 9 = 576$, mais elle est tout de même réalisable avec une matrice binaire (voir figure 5.1).

Voici le langage de base des acides aminés :

Definition R.10 (Langage de base des acides aminés)
Le langage de base des acides aminés $\mathcal{L}$ est utilisé pour décrire les modèles simples $\mathfrak{M} = \langle C, R, \Phi, V \rangle$. La syntaxe de $\mathcal{L}$ est donnée par la forme Backus-Naur suivante :

$$\phi \;:=\; p \mid \neg\phi \mid \phi \vee \phi \mid \Diamond \phi$$

où $p \in \Phi$. On utilise les abréviations standards pour les opérateurs classiques $\wedge, \to, \leftrightarrow$. En outre il est utile de stipuler :

$$\Box\phi \;:=\; \neg \Diamond \neg\phi \tag{R.3}$$

$$\Diamond^n \phi := \begin{cases} \Diamond_1 \cdots \Diamond_n \, \phi & \text{si } n > 0 \\ \phi & \text{si } n = 0 \end{cases} \tag{R.4}$$

où $n \in \mathbb{N}$. La vérité d'une proposition ϕ de $\mathcal{L}$ à un codon $c \in C$ est écrite comme

$\mathfrak{M}, c \Vdash \phi$. Voilà la sémantique de $\mathcal{L}$:

$$\mathfrak{M}, c \Vdash p \text{ ssi } c \in V(p) \quad \text{(R.5)}$$

$$\mathfrak{M}, c \Vdash \neg\phi \text{ ssi non } \mathfrak{M}, c \Vdash \phi \quad \text{(R.6)}$$

$$\mathfrak{M}, c \Vdash \phi \vee \psi \text{ ssi } \mathfrak{M}, c \Vdash \phi \text{ ou } \mathfrak{M}, c \Vdash \phi \quad \text{(R.7)}$$

$$\mathfrak{M}, c \Vdash \Diamond\phi \text{ ssi } \mathfrak{M}, c' \Vdash \phi \text{ pour quelques } c' \in C \text{ où } cRc' \quad \text{(R.8)}$$

Par exemple, le sens littéral de la proposition $\Diamond\phi$ est qu'un codon ϕ puisse être atteint par une substitution singulière ; le sens intentionnel est qu'un codon ϕ soit possible par une substitution singulière. Notez bien que la notion de possibilité biologique en jeu ici diffère des possibilités physique et logique : la substitution singulière dans le sens biologique n'est pas réflexive tandis que la substitution singulière physique ou logique est réflexive.

Cela nous donne la logique modale normale **KDBC4** qui est correcte et complète par rapport à la classe des cadres qui sont sérielles, symétriques et denses (comme le cadre du modèle simple).

Les concepts de possibilité biologique historique et de la possibilité biologique stricte peuvent être définis en termes du langage de base des acides aminés sur la base de la définition de la vérité locale et globale :

Definition R.11 (Possibilité biologique historique)
Une proposition $\phi \in \mathcal{L}$ est bio-historiquement possible à un codon $c \in C$ dans le modèle simple $\mathfrak{M} = \langle C, R, \Phi, V\rangle$ si et seulement si $\mathfrak{M}, c' \Vdash \phi$ pour quelques $c' \in C$ où cRc'.

Selon la définition R.11, la possibilité biologique historique est entièrement saisie par l'opérateur $\Diamond$ au contraire de la possibilité biologique stricte :

Definition R.12 (Possibilité biologique stricte)
Une proposition $\phi \in \mathcal{L}$ est biologiquement possible dans le modèle simple $\mathfrak{M} = \langle C, R, \Phi, V\rangle$ si et seulement si $\mathfrak{M}, c \Vdash \phi$ pour quelques $c \in C$.

En outre je montre que le modèle simple peut être simplifié davantage par contraction bisimilaire (voir définition 5.9 et figure 5.3) et je défends l'argument que la mutation silencieuse confond deux types de mutation : (1) Les mutations silencieuses inactives sont

des mutations silencieuses qui sont bisimilaires au codon du type naturel. Intuitivement, deux codons sont bisimilaires s'ils codent pour le même acide aminé et s'ils s'accordent sur les types des codons qui sont accessibles par la relation de la substitution singulière (pour une explication plus précise voir définition 5.8). Du point de vue du langage de base des acides aminés, les codons bisimilaires sont indiscernables et donc les mutations silencieuses inactives sont inactives vis-à-vis des des modalités. Autrement dit les mutations silencieuses inactives ne changent ni le phénotype actuel ni les phénotypes biologiquement possibles. (2) Par contre les mutations silencieuses actives sont des mutations silencieuses qui ne sont pas bisimilaires au codon de type naturel ; ils changent donc les phénotypes biologiquement possibles alors même que le phénotype actuel reste stable.

Modèles gradués

Dans ce chapitre je propose diverses extensions du modèle simple et du langage de base des acides aminés dans le but de tenir compte de la possibilité biologique comparative. La possibilité biologique comparative concerne la détermination d'un ordre hiérarchique des possibilités biologiques. Donc pour deux variantes v, v' d'hémoglobine causées par des substitutions singulières au codon 6 du gène *HBB*, le but est d'expliquer les conditions dans lesquelles v est plus possible que v'. Quatre distinctions au niveau concept sont distinguées :

1. Simplicité : v est plus facile à obtenir que v'.
2. Quantité : Il existe plus de possibles v que de possibles v'.
3. Processus : Il existe plus de processus pour obtenir v que pour obtenir v'.
4. Probabilité : v est plus probable que v'.

Évidemment la condition Simplicité dépend du concept de simplicité ; dans le cadre de la définition R.7, j'affirme que : v est plus facile à obtenir que v' si est seulement si le script d'édition le moins cher du type naturel à v coûte moins cher que le script d'édition le moins cher du type naturel à v'. Simplicité est implémentée par un opérateur modal interprété comme distance de Hamming (soit une certaine distance d'édition). Le cas est similaire pour Probabilité ; ici j'adopte une interprétation fréquentiste mais le modèle simple est compatible avec les autres interprétations de la probabilité. Probabilité est

implémentée par un opérateur modal probabiliste et une relation binaire pondérée (pour plus des détails voir définitions 6.2–6.4).

Je vais maintenant expliquer plus en détail les implémentations de QUANTITÉ et PROCESSUS. Lou Goble (1970) et Kit Fine (1972) on introduit l'idée de compter les états accessibles pour classer les modalités ; ici je propose deux extensions : (1) En plus d'un opérateur modal pour compter les codons qui sont accessible par des substitutions singulières relatives à un codon d'évaluation, j'introduis un opérateur modal pour compter les séquences uniques des substituions singulières qui produisent un certain acide aminé relatif à un codon d'évaluation. (2) Ces nouveaux opérateurs modaux s'étendent sur des séquences de substitutions singulières.

Voici la définition du langage compteur d'acides aminés :

Definition R.13 (Langage compteur d'acides aminés)
Le langage compteur d'acides aminés $\mathcal{L}^{\mathcal{C}}$ est utilisé pour décrire les modèles simples $\mathfrak{M} = \langle C, R, \Phi, V \rangle$. La syntaxe de $\mathcal{L}$ est donnée par la forme Backus-Naur suivante :

$$\phi \;:=\; p \mid \neg\phi \mid \phi \vee \phi \mid \delta^m_n \phi$$

où $p \in \Phi$, $\delta \in \{\Diamond, \diamondsuit\}$ et $m, n \in \mathbb{N}$. On utilise les abréviations standards pour les opérateurs classiques $\wedge, \rightarrow, \leftrightarrow$. En outre il est utile de stipuler :

$$\beta^m_n \phi \;:=\; \begin{cases} \neg \Diamond^m_n \neg\phi & \text{si } \beta = \Box \\ \neg \diamondsuit^m_n \neg\phi & \text{si } \beta = \boxdot \end{cases} \tag{R.9}$$

$$\delta^0_n \phi := \phi \tag{R.10}$$

$$\delta^m_0 \phi := \delta^m \phi \tag{R.11}$$

$$\delta!^m_n \phi := \begin{cases} \delta^m_{n-1}\phi \wedge \neg\delta!^m_n \phi & \text{si } n > 0 \\ \neg\delta^m & \text{si } n = 0 \end{cases} \tag{R.12}$$

$$\phi >^m_\delta \psi := \delta!^m_i \phi \wedge \delta!^m_j \psi \text{ et } i > j \tag{R.13}$$

$$\phi \rhd^m_\delta \psi := \bigwedge_{k=1}^{m} (\delta!^k_{i_k} \wedge \delta!^k_{j_k}) \text{ et } \sum_{k=1}^{m} i_k > \sum_{k=1}^{m} j_k \tag{R.14}$$

où $i, j \in \mathbb{N}$. La sémantique de $\mathcal{L}^{\mathcal{C}}$ est identique à la sémantique de $\mathcal{L}$ pour les propositions non-modales (voir définition R.10). Voici la sémantique des opérateurs

modaux :

$$\mathfrak{M}, c \Vdash \delta_n^m \phi \text{ ssi } \begin{cases} |\{c' : cR_1 \dots R_m c' \text{ et } \mathfrak{M}, c' \Vdash \phi\}| > n & \text{if } \delta = \Diamond \\ |\{\langle c, \dots, c' \rangle : cR_1 \dots R_m c' \text{ et } \mathfrak{M}, c' \Vdash \phi\}| > n & \text{si } \delta = \diamond\!\!\!\cdot \end{cases} \tag{R.15}$$

Considérons par exemple la condition QUANTITÉ et l'opérateur modale $\Diamond_n^m$. Il faut distinguer entre la comparaison ou classification limitée à un niveau de possibilité biologique (soit le comparateur $>_\Diamond^m$ dont le niveau est une séquence de m substitutions singulières) et la comparaison ou gradation entre des niveaux des possibilités biologiques (soit le comparateur $\rhd_\Diamond^m$ dont les niveaux vont de 1 à m). Considérons le premier comparateur. Dans le modèle simple on trouve que :

$$\text{Si } m \geq 3, \text{ alors } \gamma_{>_\Diamond^m}(p) = \gamma(p) \text{ pour toutes } p \in \Phi \tag{R.16}$$

où

$$\gamma_{>_\Diamond^m}(p) = \frac{n : \mathfrak{M}, c \Vdash \Diamond !_n^m p}{|\{c' : cR_1 \dots R_m c'\}|} \tag{R.17}$$

est la fraction de codons p qui sont accessibles par des séquences m des substitutions singulières relatives à c et

$$\gamma(p) = \frac{|V(p)|}{|C|} \tag{R.18}$$

est la fraction des codons p dans le modèle simple. Donc le contexte local du codon d'évaluation est perdu pour les possibilités biologiques à partir du troisième niveau. Autrement dit, on peut accéder à partir de c à n'importe quel codon par une séquence des trois substitutions singulières. Le nombre des codons p est identique à la taille du bloc des codons p dans le modèle simple :

$$\text{Si } \mathfrak{M} \Vdash \Diamond !_n^m p \text{ et } m \geq 3, \text{ alors } n = |V(p)| \tag{R.19}$$

Cela nous donne la classification suivante des variantes de l'hémoglobine causées par des substitutions singulières au codon 6 du gène hémoglobine beta (pour les données

numériques, voir figure 6.3) :

$$\mathfrak{M}, \mathtt{GAG} \Vdash \mathsf{D} >^{1}_{\Diamond} *, \mathsf{A}, \mathsf{E}, \mathsf{G}, \mathsf{K}, \mathsf{Q}, \mathsf{V} \tag{R.20}$$

$$\mathfrak{M}, \mathtt{GAG} \Vdash \mathsf{A}, \mathsf{G}, \mathsf{V} >^{2}_{\Diamond} *, \mathsf{D}, \mathsf{E}, \mathsf{K}, \mathsf{Q} >^{2}_{\Diamond} \mathsf{M}, \mathsf{P}, \mathsf{S}, \mathsf{T}, \mathsf{W} \tag{R.21}$$

$$\text{Si } \mathfrak{M}, \mathtt{GAG} \Vdash p >^{m}_{\Diamond} q \text{ et } m \geq 3, \text{ alors } p >_{\gamma} q \tag{R.22}$$

Modèle généralisé

Dans ce chapitre je montre en premier lieu comment les restrictions de la modélisation imposées au chapitre 4 peuvent être levées. Puis je discute quelques limitations de ma solution.

Rappelons que les modèles logiques des chapitres 5 et 6 sont limités aux variantes de l'hémoglobine causées par des substitutions singulières au codon 6 du gène *HBB*. Par une généralisation du modèle simple (voir définition R.9) on obtient des modèles logiques de n'importe quelle variante causée par n'importe quelle mutation ponctuelle à la séquence codante de n'importe quel gène.

Voici le modèle généralisé :

Definition R.14 (Modèle généralisé)
Un modèle généralisé est un quintuple $\langle G^{\mathfrak{G}}, M^{\mathfrak{G}}, R^{\mathfrak{G}}_{\mu}, \Phi^{\mathfrak{G}}, V^{\mathfrak{G}} \rangle$ où :

- $G^{\mathfrak{G}}$ est l'ensemble des gènes. Un gène $g \in G^{\mathfrak{G}}$ est représenté par une chaîne de caractères sur l'alphabet $\{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}$.
- Toute classe de mutation ponctuelle $\mu \in M^{\mathfrak{G}} = \{\text{substitution}, \text{délétion}, \text{insertion}\}$, $R^{\mathfrak{G}}_{\mu} \subseteq G^{\mathfrak{G}} \times G^{\mathfrak{G}}$ est une relation binaire interprétée comme substitution, délétion et insertion respectivement.
- $\Phi^{\mathfrak{G}}$ est l'ensemble des propositions atomiques interprété comme l'ensemble des protéines. Les minuscules p, q sans ou avec indices sont les variables de $\Phi^{\mathfrak{G}}$.
- $V^{\mathfrak{G}} : \Phi^{\mathfrak{G}} \to \mathcal{P}(G^{\mathfrak{G}})$ est une fonction d'évaluation qui assigne un ensemble des $V^{\mathfrak{G}}(p) \subseteq G^{\mathfrak{G}}$ à chaque proposition atomique $p \in \Phi^{\mathfrak{G}}$. Intuitivement l'évaluation indique pour chaque protéine les gènes qui l'encodent.

Considérons les similarités et les différences entre (1) le modèle généralisé $\mathfrak{M}^{\mathfrak{G}}$ et le modèle simple $\mathfrak{M}$ et (2) $\mathfrak{M}^{\mathfrak{G}}$ et la Bibliothèque de Mendel (voir définition R.5). (1)

Les éléments du domaine de $\mathfrak{M}^{\mathfrak{G}}$ sont des gènes alors que éléments du domaine de $\mathfrak{M}$ sont des codons ; le domaine de $\mathfrak{M}^{\mathfrak{G}}$ est plus grand de plusieurs ordres de grandeur que celui de $\mathfrak{M}$. Contrairement à $\mathfrak{M}$, $\mathfrak{M}^{\mathfrak{G}}$ n'a pas seulement une relation binaire unique interprétée comme substitution singulière, mais aussi des relations binaires interprétées comme délétion singulière et insertion singulière. Les propositions atomiques de $\mathfrak{M}^{\mathfrak{G}}$ sont des chaînes de caractères sur l'ensemble des propositions atomiques de $\mathfrak{M}$. Pour toute paire $\mathfrak{M}$ et $\mathfrak{M}^{\mathfrak{G}}$ le niveau d'ADN est encodé par le cadre alors que le niveau des protéines est encodé par l'évaluation. (2) Les éléments du domaine de $\mathfrak{M}^{\mathfrak{G}}$ sont des gènes alors que les éléments du domaine de la Bibliothèque de Mendel sont des génomes. La relation binaire de $\mathfrak{M}^{\mathfrak{G}}$ est bien définie alors que l'interprétation et la définition de la relation binaire de la Bibliothèque de Mendel sont absentes.

Voici le langage de base des protéines :

Definition R.15 (Langage de base des protéines)
Les modèles généralisés $\mathfrak{M}^{\mathfrak{G}} = \left\langle G^{\mathfrak{G}}, M^{\mathfrak{G}}, R_{\mu}^{\mathfrak{G}}, \Phi^{\mathfrak{G}}, V^{\mathfrak{G}} \right\rangle$ sont décrits par le langage de base des protéines $\mathcal{L}^{\mathcal{G}}$. La syntaxe de $\mathcal{L}^{\mathcal{G}}$ est donnée par la forme Backus-Naur suivante :

$$\phi \ := \ p \mid \neg\phi \mid \phi \vee \phi \mid \ \Diamond_{\mu} \phi$$

où $p \in \Phi^{\mathfrak{G}}$ et $\mu \in M^{\mathfrak{G}}$. On utilise les abréviations standards pour les opérateurs classiques $\wedge, \rightarrow, \leftrightarrow$. En outre il est utile de stipuler :

$$\Box_{\mu}\phi \ := \ \neg \Diamond_{\mu} \neg\phi \tag{R.23}$$

$$\langle M \rangle \phi \ := \ \Diamond_{\mu_1} \vee \cdots \vee \Diamond_{\mu_n} \phi \tag{R.24}$$

$$[M]\phi \ := \ \neg\langle M \rangle \neg\phi \tag{R.25}$$

où $n = |M^{\mathfrak{G}}|$. La vérité d'une proposition ϕ de $\mathcal{L}^{\mathcal{G}}$ à un gène $g \in G^{\mathfrak{G}}$ est écrite comme $\mathfrak{M}^{\mathfrak{G}}, g \Vdash \phi$. Voilà la sémantique de $\mathcal{L}^{\mathcal{G}}$:

$$\mathfrak{M}^{\mathfrak{G}}, g \Vdash p \text{ ssi } c \in V^{\mathfrak{G}}(p) \tag{R.26}$$

$$\mathfrak{M}^{\mathfrak{G}}, g \Vdash \neg\phi \text{ ssi non } \mathfrak{M}^{\mathfrak{G}}, g \Vdash \phi \tag{R.27}$$

$$\mathfrak{M}^{\mathfrak{G}}, g \Vdash \phi \vee \psi \text{ ssi } \mathfrak{M}^{\mathfrak{G}}, g \Vdash \phi \text{ ou } \mathfrak{M}^{\mathfrak{G}}, g \Vdash \phi \tag{R.28}$$

$$\mathfrak{M}^{\mathfrak{G}}, g \Vdash \Diamond_{\mu}\phi \text{ ssi } \mathfrak{M}^{\mathfrak{G}}, g' \Vdash \phi \text{ pour quelques } g' \in G \text{ où } gR_{\mu}^{\mathfrak{G}}g' \tag{R.29}$$

Le langage de base des protéines a quelques limitations. Les deux plus importantes sont : (1) Le langage basal des protéines est un langage propositionnel ; le pouvoir expressif

est donc limité. Par exemple, la distinction entre la possibilité biologique *de dicto* et la possibilité biologique *de re* ne peut pas être exprimée. Pour résoudre ce problème j'introduis un modèle généralisé exprimé dans un langage des protéines du premier ordre (pour plus des détails, voir les définitions 7.3 et 7.4). (2) L'opérateur $\Diamond_\mu \phi$ du langage de base des protéines est opaque : la position où les substituions, délétions ou insertions prennent place n'est pas spécifié. Cela empêche d'avoir des équivalences souhaitées, mais ce problème peut être résolu.

En conclusion, le modèle généralisé est bien supérieur à la Bibliothèque de Mendel mais présente tout de même des limitations.

SMAC

Dans ce chapitre je présente brièvement le Simple Model Amino acid Checker ou SMAC. SMAC est un outil de vérification des modèles qui est implémenté avec Python et qui est disponible pour le public sur maxghuber.github.io/SMAC sous la licence Apache. SMAC permet d'obtenir la valeur de vérité de n'importe quelle proposition dans le modèle simple $\mathfrak{M} = \langle C, R, \Phi, V \rangle$ tant local que global.

Voici une description au niveau abstrait de l'algorithme principal (pour une description plus précise, voir les définitions 8.2 et 8.3). Soit $c \in C$ le codon d'évaluation ou le codon actuel et ϕ une proposition du langage basal d'acides aminés. Il faut distinguer deux étapes.

Premièrement, la structure sémantique de ϕ dans le modèle simple est représentée par un arbre de la manière suivante : la racine a les étiquettes ϕ et c. Si ϕ est une proposition atomique, la construction de l'arbre est terminée. Sinon il suit que ϕ est soit une négation, soit une disjonction, soit une proposition modale. Si $\phi = \neg\psi$, la racine a un fils qui a ψ et c comme étiquettes. Si $\phi = \psi \vee \chi$, la racine a deux fils ; l'un a les étiquettes ψ et c et l'autre a les étiquettes χ and c. Si $\phi = \Diamond\psi$, la racine a neuf fils dont chacun a l'étiquette ψ et un codon unique qui est accessible par c via la relation de substitution singulière R. Ce processus de construction est appliqué récursivement à tous les fils de la racine (voir figure 8.1). Ainsi la complexité sémantique des étiquettes diminue strictement avec la profondeur des nœuds et les feuilles ont une proposition atomique pour une de leurs étiquettes.

Deuxièmement, l'arbre est évalué. Si la racine a une proposition atomique $p \in \Psi$ comme

étiquette, elle est désignée comme vraie si $c \in V(p)$. Sinon il suit que ϕ est soit une négation, soit une disjonction, soit une proposition modale. Si $\phi = \neg\psi$, ϕ la racine est désignée comme vraie si son fils est désigné comme vrai. Si $\phi = \psi \vee \chi$ ou $\phi = \Diamond\psi$, la racine est désignée comme vraie si un de ses fils est désigné comme vrai. Donc pour évaluer un nœud, ce processus doit être appliqué récursivement aux fils jusqu'à ce qu'on arrive aux feuilles.

Je prouve que SMAC a la propriété de la correction totale, c'est-à-dire la propriété de la correction partielle et la propriété de terminaison. En supposant des entrées correctes, une proposition bien formée ϕ et un codon d'évaluation existant $c \in C$, SMAC donne une évaluation vraie seulement si ϕ est vraie à c dans le modèle simple donc SMAC a la propriété de la correction partielle. Et SMAC s'arrête en supposant des entrées correctes donc SMAC a la propriété de terminaison (pour plus de détails voir théorème 8.1).

La performance de SMAC est sous-optimale pour les entrées de grandes tailles. Plus précisément, la durée d'exécution est déterminée par la proposition ϕ : si ϕ contient des opérateurs modaux imbriqués, la durée d'exécution a une croissance exponentielle dont l'exposant est donné par le nombre maximale n des opérateurs modaux imbriqués (soit $\mathcal{O}(2^n)$ en notation de Landau). La performance peu impressionnante de SMAC est dûe à la représentation des propositions par des arbres qui coûte chère : tous les vérifacteurs logiquement possibles sont construits. Prenons une proposition $\Diamond^n\mathsf{E}$ et négligeons les détails : l'arbre d'évaluation dont SMAC a besoin comporte au moins 9^n branches. Donc pour $n = 10$, l'arbre comporte au moins 3.5 milliards de branches. La limite pragmatique est $n = 7$ (voir figure 8.2). Or si la proposition d'entrée ne contient pas des opérateurs modaux imbriqués (par exemple la proposition $\Diamond_1\mathsf{E} \wedge \cdots \wedge \Diamond_n\mathsf{E}$), SMAC résoud la proposition en un temps polynomial (voir figure 8.2).

La performance de SMAC peut être optimisée. Par exemple au lieu de construire dans un premier temps tous les branches de l'arbre et d'effectuer l'évaluation par la suite, les branches peuvent être construites et évaluées en séquence. Donc pour un nœud avec l'étiquette $\Diamond\phi$ (ou $\phi \vee \psi$), on termine la construction des fils après avoir construit un nœud qui est désigné comme vrai (et l'inverse pour $\Box\phi$ ou $\phi \wedge \psi$). Au pire il faut quand même construire tous les branches.

Contrefactuels biologiques

Grosso modo un énoncé conditionnel contrefactuel, désigné par $\phi \rightsquigarrow \psi$, est un conditionnel où l'antécédent ϕ est faux. Par exemple, si j'avais un doctorat, alors je ne devrais pas écrire cette thèse ; ou si les cochons avaient des ailes, alors ils pourraient voler. Selon la sémantique standard des conditionnels contrefactuels de David Lewis (1973), $\phi \rightsquigarrow \psi$ est vrai dans le monde actuel (soit notre monde) si est seulement si tous les mondes ϕ les plus similaires au monde actuel sont aussi des mondes ψ (pour plus de détails, voir les définitions 9.1– 9.3). Notez qu'un monde ϕ ou ψ est un monde possible où ϕ respectivement ψ est vrai. La sémantique standard a quelques problèmes bien connus (par exemple voir Schulz 2011). Dans ce chapitre je me focalise sur les problèmes qui proviennent de l'application de la sémantique standard aux conditionnels contrefactuels biologiques, puis je propose une solution basée sur les résultats des chapitres précédents.

Le problème principal de la sémantique standard est la relation de similarité : comment peut-on déterminer si un monde possible w est plus similaire au monde actuel qu'un monde possible w' ? L'idée de Lewis (1979) est de considérer les violations des lois naturelles qui sont requis pour transformer le monde actuel en w respectivement w'. Ces violations sont appelées 'miracles'. Supposant que ni w ni w' n'est numériquement identique au monde actuel, w est donc plus similaire au monde actuel que w' si est seulement si les miracles requis pour transformer le monde actuel en w sont plus petits que les miracles requis pour transformer le monde actuel en w'. Lewis nous offre un « système de poids ou priorités » (1979: 472, ma traduction) pour juger de la taille des miracles. Appelons-le 'principe minimal des violations' (PMV en bref) :

> Il est de la plus grande importance d'éviter les violations grandes, répandues et diverses des lois. Il est d'une importance moindre de maximiser les régions spatio-temporelles dont les faits particuliers sont préservés. Il est d'une importance encore moindre d'éviter aussi les violations petites, locales et simples des lois. Il est de peu d'importance voire d'aucune de garantir la similarité approximative des faits particuliers, même concernant les faits qui nous affectent profondément (Lewis 1979: 472, ma traduction).

Les difficultés de PMV sont bien connues et ne sont donc pas rappelées ici. Mais il y a deux problèmes nouveaux portant sur les conditionnels contrefactuels biologiques. (1) Supposons que PMV est correcte. Or, pour évaluer des conditionnels contrefactuels biologiques (pour des exemples, voir chapitre 1), il faut implémenter PMV ; mais ce n'est

pas possible pour des raisons épistémiques (souvent les mondes possibles ou les miracles requis ne sont pas disponibles pour les scientifiques) et pratiques (même si les mondes possibles et les miracles étaient disponible épistémiquement, la puissance computationnelle requise ne serait pas disponible). (2) Supposons que les problèmes épistémiques et pratiques sont résolus. PMV entraîne des décalages explicatifs : PMV est formulée en termes de lois naturelles ou physiques mais ce n'est pas vrai que tous les explications biologiques peuvent être réduites aux explications en termes des lois naturelles ou physiques. Par exemple, considérons un miracle petit qui implique un changement large au niveau de la biologie. Le codon `GAG` encode la glutamine. Prenons deux variantes de `GAG` : `GAA` qui encode également la glutamine et `TAG` qui est un codon de terminaison. Selon PVM, `GAA` et `TAG` sont équisimilaires à `GAG` car le même type de miracle est requis pour transformer `GAG` en `GAA` et en `TAG`. Or, d'un point de vue biologique, `GAA` est une mutation silencieuse tandis que `TAG` est une mutation non-sens. Autrement dit, un monde glutamine est biologiquement plus similaire à un monde glutamine qu'un monde de terminaison.

Il y a trois réponses possibles : (1) Ajouter des clauses aux lois des sciences spéciales (Dunn 2011 et Dohrn et Kroedel 2013). Basé sur les arguments présentés en chapitre 2, cette réponse n'est pas disponible pour la biologie. (2) Abandonner le projet de fournir des conditions de vérité pour les conditionnelles contrefactuels biologiques (Nathan forthcoming). Cette réponse n'est pas attractive car j'ai montré ci-dessus que ces contrefactuels sont explicatifs. (3) Rejeter PVM et formuler une sémantique plus adéquate pour les conditionnelles contrefactuels biologiques. Voici ma suggestion :

Definition R.16 (Modèle adéquat)
Un modèle adéquat $\mathfrak{M}^{\mathfrak{A}}$ est un quadruple $\left\langle C^{\mathfrak{A}}, \leq_c^{\mathfrak{A}}, \Phi^{\mathfrak{A}}, V^{\mathfrak{A}} \right\rangle$ où :

- $C^{\mathfrak{A}}$ est l'ensemble des codons C (voir définition R.9).
- Pour tous $c \in C^{\mathfrak{A}}$, $\leq_c^{\mathfrak{A}}$ est un pré-ordre total sur $C^{\mathfrak{A}}$ interprété comme relation de similarité comparative relative à c.
- $\Phi^{\mathfrak{A}}$ est l'ensemble des propositions atomiques (voir définition R.9).
- $V^{\mathfrak{A}} : \Phi^{\mathfrak{A}} \to \mathcal{P}(C^{\mathfrak{A}})$ est la fonction d'évaluation V (voir définition R.9).

En bref, le principe PVM est donc remplacé par (on rappelle la définition R.7) :

$$c' \leq_c^{\mathfrak{A}} c'' \text{ ssi } \delta(c, c') \leq \delta(c, c'') \tag{R.30}$$

Voici la sémantique convenable :

Definition R.17 (Langage adéquat)
Pour décrire les modèles adéquats $\mathfrak{M}^{\mathfrak{A}} = \left\langle C^{\mathfrak{A}}, \leq_c^{\mathfrak{A}}, \Phi^{\mathfrak{A}}, V^{\mathfrak{A}} \right\rangle$ le langage adéquat $\mathcal{L}^{\mathcal{A}}$ est utilisé. La syntaxe de $\mathcal{L}^{\mathcal{A}}$ est donnée par la forme Backus-Naur suivante :

$$\phi \ := \ p \mid \neg\phi \mid \phi \vee \phi \mid \phi \rightsquigarrow \phi$$

où $p \in \Phi^{\mathcal{A}}$. On utilise les abréviations standards pour les opérateurs classiques $\wedge, \rightarrow, \leftrightarrow$. La vérité d'une proposition ϕ de $\mathcal{L}^{\mathcal{A}}$ à un codon $c \in C^{\mathfrak{A}}$ est écrite comme $\mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi$. Voilà la sémantique de $\mathcal{L}^{\mathcal{A}}$:

$$\mathfrak{M}^{\mathfrak{A}}, c \Vdash p \text{ ssi } c \in V^{\mathfrak{A}}(p) \tag{R.31}$$

$$\mathfrak{M}^{\mathfrak{A}}, c \Vdash \neg\phi \text{ ssi non } \mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi \tag{R.32}$$

$$\mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi \vee \psi \text{ ssi } \mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi \text{ ou } \mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi \tag{R.33}$$

$$\mathfrak{M}^{\mathfrak{A}}, c \Vdash \phi \rightsquigarrow \psi \text{ ssi } \forall c' \in M_{c/\phi}^{\mathfrak{A}} : \mathfrak{M}^{\mathfrak{A}}, c' \Vdash \psi \tag{R.34}$$

où $M_{c/\phi}^{\mathfrak{A}} \subseteq C^{\mathfrak{A}}$ est l'ensemble des codons ϕ maximal similaire à c:

$$c' \in M_{c/\phi}^{\mathfrak{A}} \text{ ssi } \mathfrak{M}^{\mathfrak{A}}, c' \Vdash \phi \text{ et } \neg\exists c'' \in C^{\mathfrak{A}} \text{ où } c'' <_c^{\mathfrak{A}} c' \text{ et } \mathfrak{M}^{\mathfrak{A}}, c'' \Vdash \phi \tag{R.35}$$

Pour conclure, notez que cette sémantique peut être combinée aux sémantiques construites aux chapitres 5 à 7.